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3-PYRROLYL UREA DERIVATIVES AND THEIR USE AS ANTIVIRAL AGENTS

The invention relates to substituted pyrroles and to processes for preparing them, to their use for the treatment and/or prophylaxis of diseases and also to their use for producing medicaments for the treatment and/or prophylaxis of diseases, particularly for use as antiviral agents, in particular against cytomegaloviruses.

DE-A 197 17 898 describes substituted pyrroles as additives for photographic recording material.

WO 99/23091 describes aromatic heterocyclic compounds as anti-inflammatory agents which may among other things also be suitable for treating viral infections.

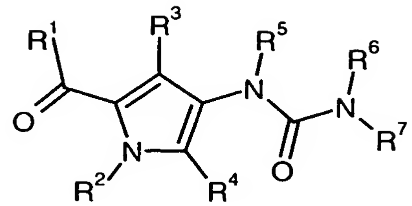
Distamycin derivatives (four pyrroles linked via amide or urea groups) are described inter alia in Possati, L. et al., *Clinical & Experimental Metastasis* **1999**, *17*(7), 575-582, Manetti, F. et al., *Journal of Computer-Aided Molecular Design* **2000**, *14*(4), 355-368 and Turpin, J. A. et al., *Expert Opinion on Therapeutic Patents* **2000**, *10*(12), 1899-1909 as anti-HIV active compounds.

Although structurally different agents with antiviral activity are on the market, development of resistance is a regular possibility. New agents for better and effective therapy are therefore desirable.

It is an object of the present invention, therefore, to provide new compounds having equal or improved antiviral action for the treatment of viral infectious diseases in humans and animals.

Surprisingly it has been found that the substituted pyrroles described in the present invention are highly active antivirally.

The present invention provides compounds of the formula



(I),

in which

R^1 is $-OR^8$ or $-NR^9R^{10}$,

R^2 is hydrogen, C_1-C_6-alkyl or aryl,

it being possible for alkyl R^2 to be substituted by 0, 1, 2 or 3 substituents R^{2-1} selected independently of one another from the group consisting of halogen, hydroxyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylcarbonyloxy, amino, C_1-C_6-alkylamino, aminocarbonyl, C_1-C_6-alkylaminocarbonyl, C_3-C_8-cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10}-aryl, phenoxy and 5- to 10-membered heteroaryl,

in which cycloalkyl, heterocyclyl, aryl or heteroaryl R^{2-1} may be substituted by 0, 1, 2 or 3 substituents selected independently of one another from the group consisting of halogen, hydroxyl, oxo, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl, C_1-C_6-alkylaminocarbonyl and phenyl,

it being possible for aryl R^2 to be substituted by 0, 1, 2 or 3 substituents R^{2-2} selected independently of one another from the group consisting of halogen, hydroxyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl, C_1-C_6-alkylaminocarbonyl, C_3-C_8-cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10}-aryl and 5- to 10-membered heteroaryl,

R^3 and R^4 independently of one another are hydrogen or C_1-C_6-alkyl,

R^5 and R^6 independently of one another are hydrogen or C_1-C_6-alkyl,

R^7 is 3- to 12-membered carbocyclyl,

it being possible for the carbocyclyl to be substituted by 0, 1, 2, 3, 4 or 5 substituents selected independently of one another from the group consisting of halogen, hydroxyl, C_1-C_6-alkyl and C_1-C_6-alkoxy,

R^8 is hydrogen or C_1-C_6-alkyl,

it being possible for alkyl R^8 to be substituted by 0, 1, 2 or 3 substituents R^{8-1} selected independently of one another from the group consisting of hydroxyl, amino, C_1-C_6-alkoxy, C_1-C_6-alkylamino, aminocarbonyl, C_1-C_6-alkylcarbonylamino, C_3-C_8-cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10}-aryl and 5- to 10-membered heteroaryl,

in which cycloalkyl, heterocyclyl, aryl or heteroaryl R^{8-1} may be substituted by 0, 1, 2 or 3 substituents selected independently of one another from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl and C_1-C_6-alkylaminocarbonyl,

R^9 is hydrogen or C_1-C_6-alkyl,

it being possible for alkyl R^9 to be substituted by 0 or 1 substituent R^{9-1} selected from the group consisting of hydroxyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl, C_1-C_6-alkylaminocarbonyl, C_3-C_8-cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10}-aryl and 5- to 10-membered heteroaryl,

in which cycloalkyl, heterocyclyl, aryl or heteroaryl R^{9-1} may be substituted by 0, 1, 2 or 3 substituents selected independently of one another from the group consisting of halogen, hydroxyl, nitro, cyano, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl and C_1-C_6-alkylaminocarbonyl,

and

R^{10} is hydrogen, C_1-C_6-alkyl, C_3-C_8-cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10}-aryl or 5- to 10-membered heteroaryl,

it being possible for alkyl R^{10} to be substituted by 0, 1, 2 or 3 substituents R^{10-1} selected independently of one another from the group consisting of halogen, hydroxyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl, C_1-C_6-alkylaminocarbonyl, C_3-C_8-cycloalkyl, 5- to 10-membered heterocyclyl, C_6-C_{10}-aryl and 5- to 10-membered heteroaryl,

in which cycloalkyl, heterocyclyl, aryl or heteroaryl R^{10-1} may be substituted by 0, 1, 2 or 3 substituents selected independently of one another from the group consisting of halogen, hydroxyl, oxo, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl and C_1-C_6-alkylaminocarbonyl,

it being possible for cycloalkyl, heterocyclyl, aryl or heteroaryl R^{10} to be substituted by 0, 1, 2 or 3 substituents R^{10-2} selected independently of one another from the group consisting of halogen, hydroxyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl and C_1-C_6-alkylaminocarbonyl,

or

R^9 and R^{10} together with the nitrogen atom to which they are attached form a 4- to 8-membered heterocycle which may contain up to two further heteroatoms from the series N, O and/or S,

it being possible for the heterocycle to be substituted by 0, 1, 2 or 3 substituents selected independently of one another from the group consisting of halogen, hydroxyl, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl and C_1-C_6-alkylaminocarbonyl,

and their salts, their solvates and the solvates of their salts.

Compounds of the invention are the compounds of the formula (I) and their salts, solvates and solvates of the salts, compounds referred to below as exemplary embodiment(s) and their salts, solvates and solvates of the salts, where the compounds which are encompassed by formula (I) and are referred to below are not already salts, solvates and solvates of the salts.

The compounds of the invention may, depending on their structure, exist in stereoisomeric forms (enantiomers, diastereomers). The invention therefore provides the enantiomers or diastereomers and their respective mixtures. From such mixtures of enantiomers and/or diastereomers it is possible to isolate the stereoisomerically pure constituents in a known manner.

Where the compounds of the invention can occur in tautomeric forms the present invention embraces all tautomeric forms.

Salts preferred for the purposes of the present invention are physiologically acceptable salts of the compounds of the invention. Also embraced, however, are salts which, though not themselves suitable for pharmaceutical applications, can nevertheless be used, for example, for isolating or purifying the compounds of the invention.

Physiologically acceptable salts of the compounds of the invention embrace acid addition salts of mineral acids, carboxylic acids and sulfonic acids, examples being salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, benzenesulfonic acid, naphthalenedisulfonic acid, acetic acid, trifluoroacetic acid, propionic acid, lactic acid, tartaric acid, malic acid, citric acid, fumaric acid, maleic acid and benzoic acid.

Physiologically acceptable salts of the compounds of the invention also embrace salts of customary bases, such as, by way of example and preferably, alkali metal salts (e.g. sodium and potassium salts), alkaline earth metal salts (e.g. calcium and magnesium salts), and ammonium salts derived from ammonia or organic amines having 1 to 16 carbon atoms, such as, by way of example and preferably, ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine, triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methylmorpholine, arginine, lysine, ethylenediamine and N-methylpiperidine.

Solvates refer for the purposes of the invention to those forms of the compounds of the invention which in the solid or liquid state form a complex through coordination with solvent molecules. Hydrates are one specific form of the solvates, in which the coordination takes place with water.

For the purposes of the present invention the substituents, unless otherwise specified, have the following definition:

Alkyl per se and "alk" and "alkyl" in alkoxy, alkylamino, alkylcarbonyl, alkylcarbonyloxy and alkoxycarbonyl are a linear or branched alkyl radical having generally 1 to 6 ("C_1-C_6-alkyl"), preferably 1 to 4, more preferably 1 to 3 carbon atoms, by way of example and preferably methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-pentyl and n-hexyl.

Alkoxy is, by way of example and preferably, methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy and n-hexoxy.

Alkylamino is an alkylamino radical having one or two alkyl substituents (chosen independently of one another), by way of example and preferably methylamino, ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino, n-hexylamino, *N,N*-dimethylamino, *N,N*-diethylamino, *N*-ethyl-*N*-methylamino, *N*-methyl-*N*-n-propylamino, *N*-isopropyl-*N*-n-propylamino, *N*-t-butyl-*N*-methylamino, *N*-ethyl-*N*-n-pentylamino and *N*-n-hexyl-*N*-methylamino. C_1-C_3-alkylamino is for example a monoalkylamino radical having 1 to 3 carbon atoms or a dialkylamino radical having 1 to 3 carbon atoms per alkyl substituent.

Alkylcarbonyl is, by way of example and preferably, acetyl and propanoyl.

Alkylcarbonyloxy is, by way of example and preferably, methylcarbonyloxy, ethylcarbonyloxy, n-propylcarbonyloxy, isopropylcarbonyloxy, tert-butylcarbonyloxy, n-pentylcarbonyloxy and n-hexylcarbonyloxy.

Alkoxycarbonyl is, by way of example and preferably, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, tert-butoxycarbonyl, n-pentoxycarbonyl and n-hexoxycarbonyl.

Alkylaminocarbonyl is an alkylaminocarbonyl radical having one or two alkyl substituents (chosen independently of one another), by way of example and preferably

methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, n-hexylaminocarbonyl, *N,N*-dimethylaminocarbonyl, *N,N*-diethylaminocarbonyl, *N*-ethyl-*N*-methylaminocarbonyl, *N*-methyl-*N*-n-propylaminocarbonyl, *N*-isopropyl-*N*-n-propylaminocarbonyl, *N*-tert-butyl-*N*-methylaminocarbonyl, *N*-ethyl-*N*-n-pentylaminocarbonyl and *N*-n-hexyl-*N*-methylaminocarbonyl. C_1-C_3-alkylaminocarbonyl is for example a monoalkylaminocarbonyl radical having 1 to 3 carbon atoms or a dialkylaminocarbonyl radical having 1 to 3 carbon atoms per alkyl substituent.

<u>Alkylcarbonylamino</u> is, by way of example and preferably, methylcarbonylamino, ethylcarbonylamino, n-propylcarbonylamino, isopropylcarbonylamino, tert-butylcarbonylamino, n-pentylcarbonylamino and n-hexylcarbonylamino.

<u>Aryl</u> is a mono- to tricyclic aromatic, carbocyclic radical having generally 6 to 14 carbon atoms; by way of example and preferably, phenyl, naphthyl and phenanthrenyl.

<u>5- to 10-membered heteroaryl</u> for the purposes of the invention is generally an aromatic, mono- or bicyclic radical having 5 to 10 ring atoms and up to 5 heteroatoms from the series S, O and/or N. Preference is given to 5- to 6-membered heteroaryls having up to 4 heteroatoms. The heteroaryl radical may be attached via a carbon atom or heteroatom. By way of example and preferably mention may be made of the following: thienyl, furyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, pyridyl, pyrimidyl, pyridazinyl, indolyl, indazolyl, benzofuranyl, benzothiophenyl, quinolinyl and isoquinolinyl.

<u>Cycloalkyl</u> is a cycloalkyl group having generally 3 to 8, preferably 3 to 6, carbon atoms, by way of example and preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

<u>3- to 12-membered carbocyclyl</u> is a mono- or polycyclic, carbocyclic radical having 3 to 12 ring atoms. 3- to 10-membered, especially 4- to 8-membered, carbocyclyl are preferred. Mono- or bicyclic carbocyclyl is preferred. The carbocyclyl radicals may be saturated or partly unsaturated. Saturated carbocyclyl radicals are preferred. By way of example and preferably mention may be made of the following: cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl, cyclooctenyl, cyclononyl, cyclononenyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl,

bicyclo[3.2.1]octyl, bicyclo[2.2.2]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[3.3.2]decyl, bicyclo[4.3.1]decyl, adamant-1-yl, adamant-2-yl, bicyclo[2.2.1]heptenyl, bicyclo[2.2.2]octenyl and bicyclo[3.2.2]nonenyl.

5- to 10-membered heterocyclyl is for the purposes of the invention a mono- or bicyclic, saturated or partly unsaturated heterocycle having up to three heteroatoms from the series N, O and/or S, which is attached via a ring carbon atom or a nitrogen atom of the heterocycle. By way of example and preferably mention may be made of the following: tetrahydrofuryl, dihydrofuryl, imidazolidinyl, thiolanyl, dioxolanyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, dihydropyranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, 7-oxabicyclo[2.2.1]heptanyl and 7-oxabicyclo[2.2.1]hept-5-enyl.

A 4- to 8-membered heterocycle having at least one ring nitrogen atom is for the purposes of the invention a saturated or partly unsaturated, monocyclic heterocycle which may contain up to two further heteroatoms from the series N, O and/or S and is attached via a ring nitrogen atom of the heterocycle. Preference is given to a 5- to 7-membered, saturated, monocyclic N-heterocycle which may contain a second nitrogen atom or an oxygen atom as a further heteroatom. By way of example and preferably mention may be made of the following: pyrrolidinyl, pyrrolinyl, oxazolidinyl, thiazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, hexahydroazepinyl, hexahydro-1,4-diazepinyl, octahydroazocinyl.

Halogen is fluorine, chlorine, bromine and iodine.

An * symbol on a carbon atom means that the compound, in terms of the configuration at this carbon atom, is in enantiopure form, by which is meant for the purposes of the present invention an enantiomeric excess of more than 90% (> 90% ee).

Preference is given for the purposes of the present invention to compounds of the formula (I)

in which

R^1 is $-OR^8$ or $-NR^9R^{10}$,

R^2 is hydrogen or C_1-C_4-alkyl,

it being possible for alkyl R^2 to be substituted by 0 or 1 substitutent R^{2-1} selected from the group consisting of hydroxyl, C_1-C_6-alkoxy, C_1-C_6-alkylcarbonyloxy, C_1-C_6-alkylaminocarbonyl, C_3-C_7-cycloalkyl, 5- to 6-membered heterocyclyl, phenyl, phenoxy and 5- to 6-membered heteroaryl,

in which cycloalkyl, heterocyclyl, phenyl or heteroaryl R^{2-1} may be substituted by 0, 1, 2 or 3 substituents selected independently of one another from the group consisting of halogen, hydroxyl, oxo, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl, C_1-C_6-alkylaminocarbonyl and phenyl,

R^3 and R^4 are hydrogen,

R^5 and R^6 are hydrogen,

R^7 is 6- to 8-membered carbocyclyl,

it being possible for carbocyclyl R^7 to be substituted by 0, 1, 2, 3 or 4 substituents selected independently of one another from the group consisting of C_1-C_6-alkyl,

R^8 is C_1-C_4-alkyl,

it being possible for alkyl R^8 to be substituted by 0, 1 or 2 substituents R^{8-1} selected independently of one another from the group consisting of hydroxyl, amino, C_1-C_6-alkoxy, C_1-C_6-alkylamino, aminocarbonyl, C_1-C_6-alkylcarbonylamino, pyridyl, 1,2,4-triazol-1-yl and pyrazol-1-yl,

R^9 is hydrogen or C_1-C_6-alkyl,

it being possible for alkyl R^9 to be substituted by 0 or 1 substituent R^{9-1} selected from the group consisting of hydroxyl, C_1-C_6-alkoxy and amino,

and

R^{10} is hydrogen, C_1-C_6-alkyl, C_3-C_6-cycloalkyl or phenyl,

it being possible for alkyl R^{10} to be substituted by 0 or 1 substituent R^{10-1} selected from the group consisting of hydroxyl, C_1-C_6-alkoxy, C_1-C_6-alkylamino, C_5-C_7-cycloalkyl, 5- to 6-membered heterocyclyl, phenyl and 5- to 6-membered heteroaryl,

in which cycloalkyl, heterocyclyl, phenyl or heteroaryl R^{10-1} may be substituted by 0, 1, 2 or 3 substituents selected independently of one another from the group consisting of halogen, hydroxyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl and C_1-C_6-alkylaminocarbonyl,

or

R^9 and R^{10} together with the nitrogen atom to which they are attached form a 5- to 6-membered heterocycle which may contain up to two further heteroatoms from the series N, O and/or S,

and their salts, their solvates and the solvates of their salts.

Preference for the purposes of the present invention is also given to compounds of the formula (I),

in which

R^1 is $-OR^8$ or $-NR^9R^{10}$,

R^2 is hydrogen or C_1-C_4-alkyl,

it being possible for alkyl R^2 to be substituted by 0 or 1 substituent R^{2-1} selected from the group consisting of methoxy, diethylaminocarbonyl, cyclopropyl, phenyl, phenoxy and pyridyl,

in which phenyl R^{2-1} may be substituted by 0, 1 or 2 substituents selected independently of one another from the group consisting of fluorine, chlorine, nitro, cyano, trifluoromethyl, methyl, methoxy and methyloxycarbonyl,

R^3 and R^4 are hydrogen,

R^5 and R^6 are hydrogen,

R^7 is bicyclo[2.2.1]heptyl,

it being possible for bicyclo[2.2.1]heptyl to be substituted by 0, 1, 2, 3 or 4 methyl groups,

R^8 is C_1-C_3-alkyl,

it being possible for alkyl R^8 to be substituted by 0 or 1 substituent R^{8-1} selected independently of one another from the group consisting of hydroxyl, dimethylamino, aminocarbonyl, methylcarbonylamino, pyridyl, 1,2,4-triazol-1-yl and pyrazol-1-yl,

R^9 is hydrogen,

and

R^{10} is hydrogen, C_1-C_4-alkyl, cyclopropyl or cyclopentyl,

it being possible for alkyl R^{10} to be substituted by 0 or 1 substituent R^{10-1} selected from the group consisting of hydroxyl, methoxy, dimethylamino, phenyl, pyridyl and imidazol-1-yl,

in which phenyl R^{10-1} may be substituted by 0, 1 or 2 methoxy substituents,

and their salts, their solvates and the solvates of their salts.

Preference is given for the purposes of the present invention to compounds of the formula (I),

in which

R^1 is $-OR^8$ or $-NR^9R^{10}$,

R^2 is hydrogen or C_1-C_3-alkyl,

it being possible for alkyl R^2 to be substituted by 0 or 1 substituent R^{2-1} selected from the group consisting of C_5-C_7-cycloalkyl, 5- to 6-membered heterocyclyl, phenyl and 5- to 6-membered heteroaryl,

in which cycloalkyl, heterocyclyl, phenyl or heteroaryl R^{2-1} may be substituted by 0, 1, 2 or 3 substituents selected independently of one another from the group consisting of halogen, hydroxyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl and C_1-C_6-alkylaminocarbonyl,

R^3 and R^4 are hydrogen,

R^5 and R^6 are hydrogen,

R^7 is 6- to 8-membered carbocyclyl,

it being possible for carbocyclyl R^7 to be substituted by 0, 1, 2, 3 or 4 substituents selected independently of one another from the group consisting of C_1-C_6-alkyl,

R^8 is C_1-C_4-alkyl,

it being possible for alkyl R^8 to be substituted by 0, 1 or 2 substituents R^{8-1} selected independently of one another from the group consisting of hydroxyl, amino and C_1-C_6-alkoxy,

R^9 is hydrogen or C_1-C_6-alkyl,

it being possible for alkyl R^9 to be substituted by 0 or 1 substituent R^{9-1} selected from the group consisting of hydroxyl, C_1-C_6-alkoxy and amino,

and

R^{10} is hydrogen or C_1-C_6-alkyl,

it being possible for alkyl R^{10} to be substituted by 0 or 1 substituent R^{10-1} selected from the group consisting of C_5-C_7-cycloalkyl, 5- to 6-membered heterocyclyl, phenyl and 5- to 6-membered heteroaryl,

in which cycloalkyl, heterocyclyl, phenyl or heteroaryl R^{10-1} may be substituted by 0, 1, 2 or 3 substituents selected independently of one another from the group consisting of halogen, hydroxyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_1-C_6-alkyl, C_1-C_6-alkoxy, hydroxycarbonyl, C_1-C_6-alkoxycarbonyl, amino, C_1-C_6-alkylamino, aminocarbonyl and C_1-C_6-alkylaminocarbonyl,

and their salts, their solvates and the solvates of their salts.

Preference for the purposes of the present invention is also given to compounds of the formula (I),

in which

R^1 is $-OR^8$ or $-NR^9R^{10}$,

R^2 is hydrogen or benzyl,

R^3 and R^4 are hydrogen,

R^5 and R^6 are hydrogen,

R^7 is bicyclo[2.2.1]heptyl,

it being possible for bicyclo[2.2.1]heptyl to be substituted by 0, 1, 2, 3 or 4 methyl groups,

R^8 is methyl or ethyl,

R^9 is hydrogen,

and

R^{10} is hydrogen or benzyl,

and their salts, their solvates and the solvates of their salts.

Preference for the purposes of the present invention is also given to compounds of the formula (I) in which R^1 is $-OR^8$ and R^8 is methyl or ethyl.

Preference for the purposes of the present invention is also given to compounds of the formula (I) in which R^1 is $-NR^9R^{10}$, R^9 is hydrogen and R^{10} is hydrogen or benzyl.

Preference for the purposes of the present invention is also given to compounds of the formula (I) in which R^2 is hydrogen.

Preference for the purposes of the present invention is also given to compounds of the formula (I) in which R^3, R^4, R^5 and R^6 are hydrogen.

Preference for the purposes of the present inventions is also given to compounds of the formula (I) in which R^7 is adamantyl.

Preference for the purposes of the present inventions is also given to compounds of the formula (I) in which R^7 is bicyclo[2.2.1]heptyl, it being possible for bicyclo[2.2.1]heptyl to be substituted by 0, 1, 2, 3 or 4 methyl groups.

Preference here is given to compounds of the formula (I) in which R^7 is bicyclo[2.2.1]heptyl, bicyclo[2.2.1]heptyl being substituted by 3 methyl groups.

Particular preference is given here to compounds of the formula (I) in which R^7 is 1,7,7-trimethylbicyclo[2.2.1]hept-2-yl.

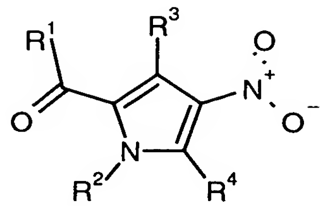
Very particular preference is given here to compounds of the formula (I) in which R^7 is (1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl, (1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl, (1R,2R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl or (1S,2S,4S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl, and mixtures thereof, particularly the mixtures of enantiomers (1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl and (1S,2R,4S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl and also of the enantiomers (1R,2R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl and (1S,2S,4S)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl.

Upmost preference is given here to compounds of the formula (I) in which R^7 is (1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl.

The invention further provides a process for preparing the compounds of the formula (I), where

according to process [A]

compounds of the formula



(IIa),

in which

R^1 is $-OR^8$,

R^8 is the optionally substituted alkyl indicated for R^8 in formula (I), and

R^2, R^3 and R^4 are as defined above,

are reacted in the first stage with a reducing agent,

in the second stage optionally with compounds of the formula

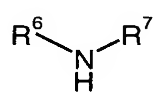
$$X^1\text{-}R^5 \quad \text{(III)},$$

in which

R^5 is as defined above and

X^1 is halogen, preferably bromine or chlorine,

and in the third stage, in the presence of a carbonic acid derivative, with compounds of the formula

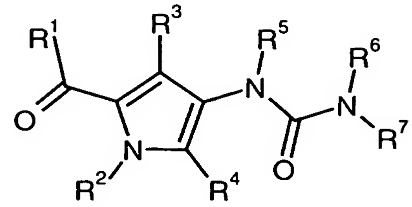


(IV),

in which

R^6 and R^7 are as defined above,

to give compounds of the formula



(Ia),

in which

R^1 is $-OR^8$,

R^8 has the definition as in formula (IIa), and

R^2, R^3, R^4, R^5, R^6 and R^7 are as defined above,

or

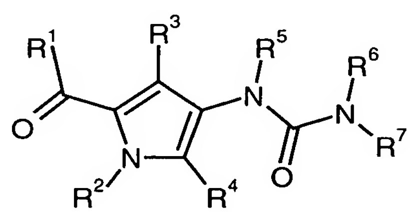
according to process [B]

compounds of the formula (Ia)

in which

R^8 is methyl or ethyl,

are reacted in the presence of bases to give compounds of the formula



(Ib),

in which

R^1 is $-OR^8$,

R^8 is hydrogen, and

R^2, R^3, R^4, R^5, R^6 and R^7 are as defined above,

or

according to process [C]

compounds of the formula (Ib) are reacted with compounds of the formula

$$R^1\text{-H} \quad (V),$$

in which

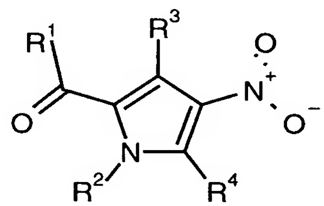
R^1 is as defined above,

in the presence of dehydrating reagents to give compounds of the formula (I),

or

according to process [D]

compounds of the formula



(IIb),

in which

R^1 is $-NR^9R^{10}$, and

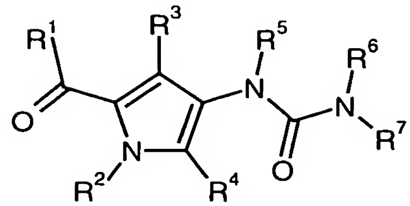
R^2, R^3, R^4, R^9 and R^{10} are as defined above,

are reacted in the first stage with a reducing agent,

in the second stage optionally with compounds of the formula (III)

and in the third stage, in the presence of a carbonic acid derivative, with compounds of the formula (IV)

to give compounds of the formula



(Ic),

in which

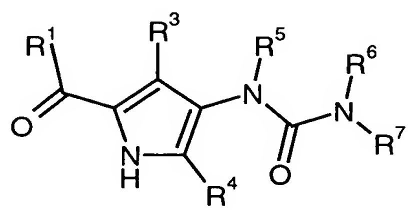
R^1 is $-NR^9R^{10}$, and

R^2, R^3, R^4, R^5, R^6, R^7, R^9 and R^{10} are as defined above,

or

according to process [E]

compounds of the formula



(Id),

in which

R^1, R^3, R^4, R^5, R^6 and R^7 are as defined above,

are reacted with compounds of the formula

$$X^2\text{-}R^2 \qquad \text{(VIII)},$$

in which

R^2 is as defined above, and

X^2 is halogen, preferably bromine or chlorine,

to give compounds of the formula (I).

Formula (I) embraces the compounds (Ia), (Ib), (Ic) and (Id).

Formula (II) embraces the compounds (IIa) and (IIb).

The compounds of the formula (III), (IV), (V) and (VIII) are known or can be synthesized by known processes from the corresponding reactants.

The following applies to processes [A] and [D]:

1st stage:

The reaction takes place in general in inert solvents, preferably in a temperature range from 0°C up to the reflux of the solvents under atmospheric pressure up to 3 bar.

Reducing agents are, for example, palladium on active carbon and hydrogen, formic acid/triethylamine/palladium on active carbon, zinc, zinc/hydrochloric acid, iron, iron/hydrochloric acid, iron(II) sulfate/hydrochloric acid, sodium sulfide, sodium disulfide sodium dithionite, ammonium polysulfide, sodium borohydride/nickel chloride, tin dichloride, titanium trichloride or Raney nickel and aqueous hydrazine solution, preference being given to Raney nickel and aqueous hydrazine solution.

Inert solvents are, for example, ethers such as diethyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol or tert-butanol, hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane or petroleum fractions, or other solvents such as dimethylformamide, dimethylacetamide, acetonitrile or pyridine, and, in the case of water-miscible solvents, mixtures thereof with water; a preferred solvent is methanol, ethanol, isopropanol or, in the case of Raney nickel and aqueous hydrazine solution, tetrahydrofuran.

2nd stage:

The reaction takes place in general in inert solvents, optionally in the presence of a base, preferably in a temperature range from -20°C to 40°C under atmospheric pressure.

Bases are, for example, amides such as sodium amide, lithium hexamethyldisilazide, potassium hexamethyldisilazide, lithium diisopropylamide, or other bases such as sodium hydride, DBU or diisopropylethylamine, preferably sodium amide, lithium hexamethyldisilazide, potassium hexamethyldisilazide or lithium diisopropylamide.

Inert solvents are, for example, ethers, such as diethyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, hydrocarbons such as benzene, ethylbenzene, xylene, toluene, preferably tetrahydrofuran or toluene.

3rd stage:

The reaction takes place in general in inert solvents, preferably in a temperature range from room temperature up to 40°C under atmospheric pressure.

Carbonic acid derivatives are, for example, N,N-carbonyldiimidazole, phosgene, diphosgene, triphosgene, phenyl chloroformate or 4-nitrophenyl chloroformate, preference being given to N,N-carbonyldiimidazole.

Inert solvents are, for example, halogenated hydrocarbons such as methylene chloride, trichloromethane, tetrachloromethane, trichloroethane, tetrachloroethane, 1,2-dichloroethane or trichloroethylene, ethers such as diethyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane or petroleum fractions, or other solvents such as ethyl acetate, acetone, dimethylformamide, dimethylacetamide, 2-butanone, dimethyl sulfoxide, acetonitrile or pyridine, and, in the case of water-miscible solvents, mixtures thereof with water, preference being given to dimethyl sulfoxide.

The following applies to process [B]:

The reaction takes place in general in inert solvents, preferably in a temperature range from 0°C up to the reflux of the solvents under atmospheric pressure.

Bases are, for example, alkali metal hydroxides such as sodium, lithium or potassium hydroxide, or alkali metal carbonates such as cesium carbonate, sodium or potassium carbonate, preferably sodium hydroxide.

Inert solvents are, for example, halogenated hydrocarbons such as methylene chloride, trichloromethane, tetrachloromethane, trichloroethane, tetrachloroethane, 1,2-dichloroethane or trichloroethylene, ethers such as diethyl ether, methyl tert-butyl ether,

1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethylether or diethylene glycol dimethyl ether, alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol or tert-butanol, hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane or petroleum fractions, or other solvents such as dimethylformamide, dimethylacetamide, dimethyl sulfoxide, acetonitrile or pyridine, or mixtures of solvents with water; preference as solvent is given to a mixture of ethanol and water.

The following applies to process [C]:

The reaction takes place in general in inert solvents, optionally in the presence of a base, preferably in a temperature range from -70°C to 40°C under atmospheric pressure.

Suitable dehydrating reagents in this case are, for example, carbodiimides such as N,N'-diethyl-, N,N,'-dipropyl-, N,N'-diisopropyl-, N,N'-dicyclohexylcarbodiimide, N-(3-dimethylaminoisopropyl)-N'-ethylcarbodiimide hydrochloride (EDC), N-cyclohexylcarbodiimide-N'-propyloxymethyl-polystyrene (PS-carbodiimide) or carbonyl compounds such as carbonyldiimidazole, or 1,2-oxazolium compounds such as 2-ethyl-5-phenyl-1,2-oxazolium 3-sulfate or 2-tert-butyl-5-methylisoxazolium perchlorate, or acylamino compounds such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline, or propanephosphonic anhydride, or isobutyl chloroformate, or bis(2-oxo-3-oxazolidinyl)phosphoryl chloride or benzotriazolyloxytri(dimethylamino)phosphonium hexafluorophosphate, or O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), 2-(2-oxo-1-(2H)-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TPTU) or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), or 1-hydroxybenzotriazole (HOBt), or benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), or mixtures of these, with bases.

Bases are, for example, alkali metal carbonates, such as sodium or potassium carbonate, or sodium or potassium hydrogen carbonate, or organic bases such as trialkylamines, for example triethylamine, N-methylmorpholine, N-methylpiperidine, 4-dimethylaminopyridine or diisopropylethylamine, or DBU, DBN, pyridine; triethylamine is preferred.

Preferably the condensation is carried out with carbonyldiimidazole.

Inert solvents are, for example, halogenated hydrocarbons such as methylene chloride, trichloromethane, tetrachloromethane, trichloroethane, tetrachloroethane, 1,2-dichloroethane or trichloroethylene, ethers such as diethyl ether, methyl tert-butylether, 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane or petroleum fractions, or other solvents such as ethyl acetate, acetone, dimethylformamide, dimethylacetamide, 2-butanone, dimethyl sulfoxide, acetonitrile or pyridine, and, in the case of water-miscible solvents, mixtures thereof with water, preference being given to dimethylformamide.

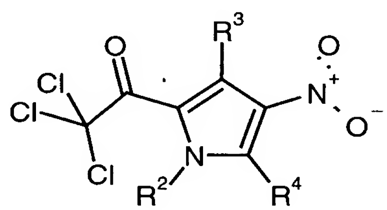
The following applies to process [E]:

The reaction takes place in general in inert solvents, in the presence of a base, preferably in a temperature range from -20°C to 40°C under atmospheric pressure.

Bases are, for example, amides such as sodium amide, lithium hexamethyldisilazide, potassium hexamethyldisilazide, lithium diisopropylamide, or other bases such as sodium hydride, DBU, diisopropylethylamine or potassium tert-butoxide, preference being given to potassium tert-butoxide.

Inert solvents are, for example, ethers such as diethyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, hydrocarbons such as benzene, ethylbenzene, xylene, toluene, or other solvents such as dimethylformamide, preference being given to dimethylformamide.

The compounds of the formula (II) are known or can be prepared by reacting compounds of the formula



(VI),

in which

R^2, R^3 and R^4 are as defined above,

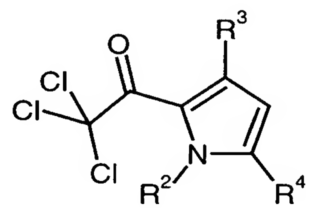
with compounds of the formula (V).

The reaction takes place in general in inert solvents, optionally in the presence of a base, preferably in a temperature range from room temperature to 40°C under atmospheric pressure.

Bases are, for example, alkali metal carbonates such as cesium carbonate, sodium or potassium carbonate, or potassium tert-butoxide, or other bases such as sodium hydride, DBU, triethylamine or diisopropylethylamine, preference being given to diisopropylethylamine and triethylamine.

Inert solvents are, for example, halogenated hydrocarbons such as methylene chloride, trichloromethane, tetrachloromethane, trichloroethane, tetrachloroethane, 1,2-dichloroethane or trichloroethylene, ethers such as diethyl ether, methyl tert-butylether, 1,2-dimethoxyethane, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol or tert-butanol, hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane or petroleum fractions, or other solvents such as ethyl acetate, acetone, dimethylformamide, dimethylacetamide, 2-butanone, dimethyl sulfoxide, acetonitrile or pyridine, preference being given to ethanol and tetrahydrofuran.

The compounds of the formula (VI) are known or can be prepared by reacting compounds of the formula



(VII),

in which

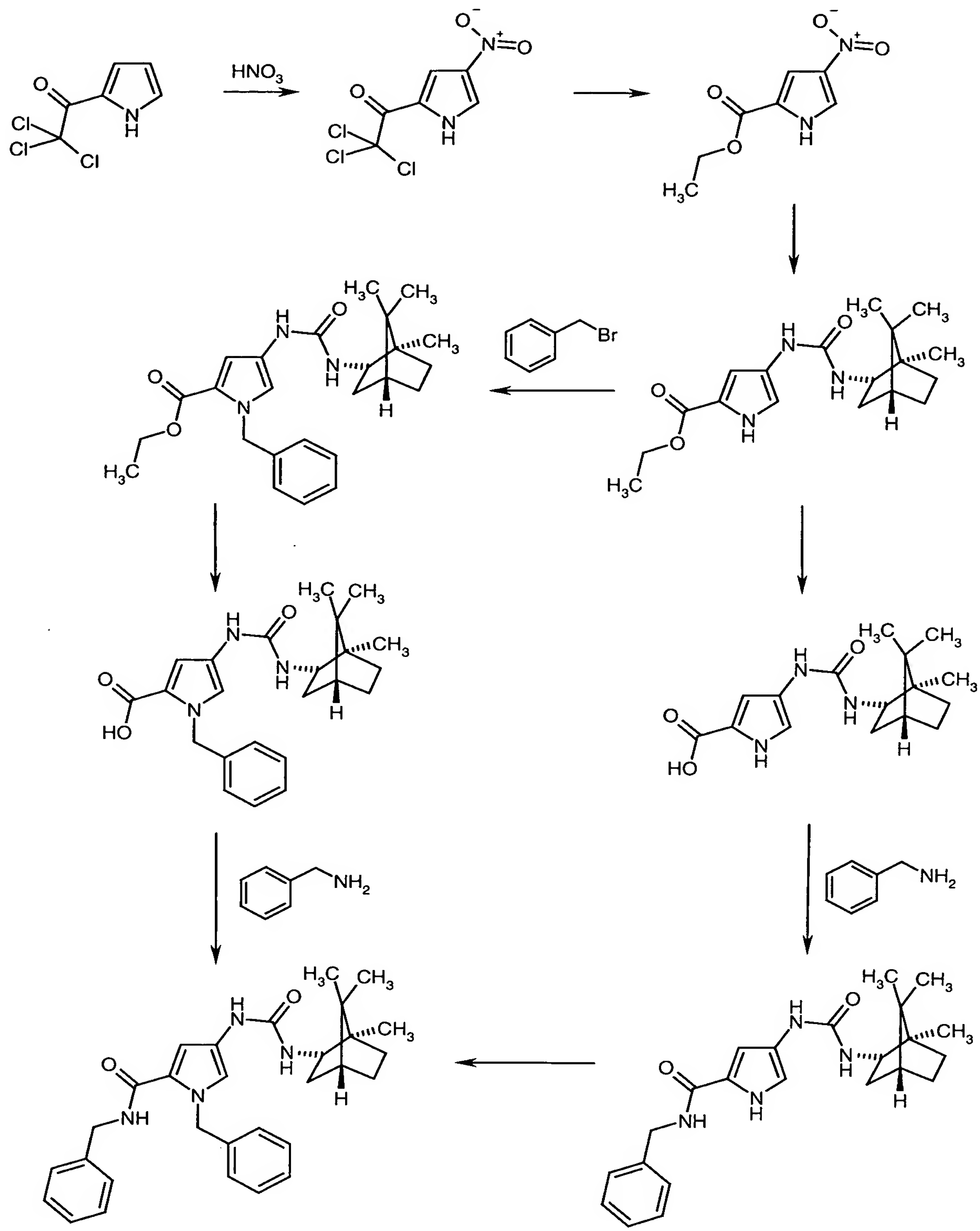
R^2, R^3 and R^4 are as defined above,

with fuming nitric acid, concentrated nitric acid, nitrating acid or other proportions of sulfuric acid and nitric acid, optionally in acetic anhydride as solvent, preferably in a temperature range from -60°C to 0°C under atmospheric pressure.

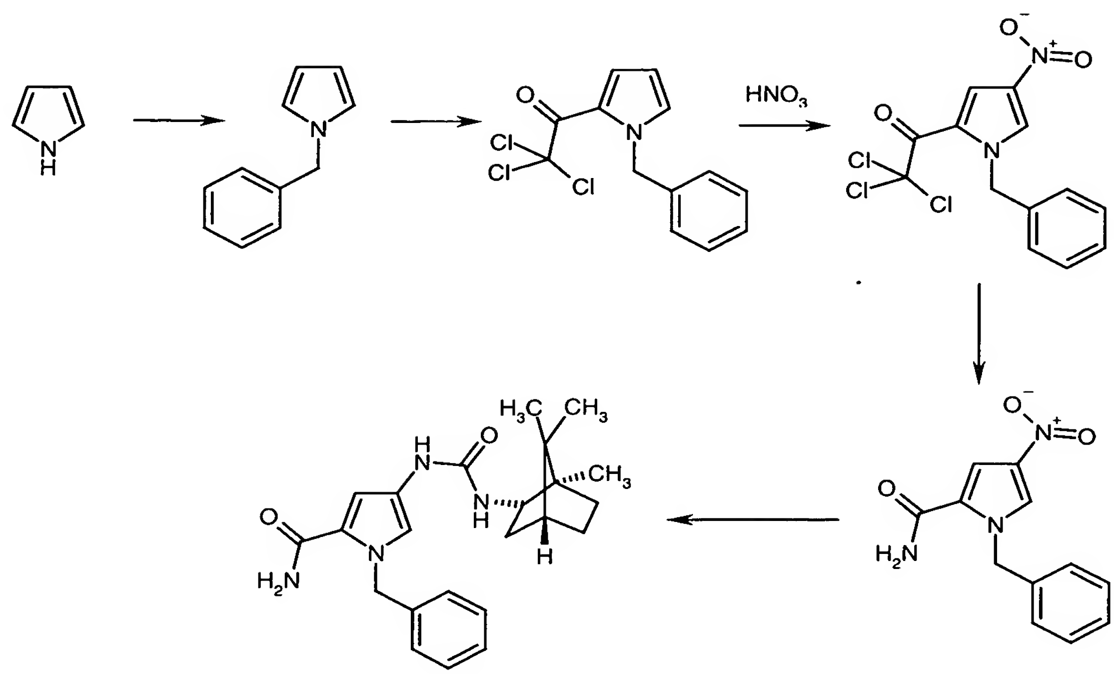
The compounds of the formula (VII) are known or can be synthesized by known processes from the corresponding reactants.

The introduction of the substituent R^2 by alkylating methods that are known to the skilled worker may take place, depending on the substitution pattern of the pyrrole, at different points on the synthesis route.

Synthesis scheme 1:


HNO3
Cl
Cl
Cl
O
N
H
O
N
O
H3C
CH3
CH3
Br
HO
NH
NH2

Synthesis scheme 2:



The compounds of the general formula (I) according to the invention exhibit an unforeseeable, surprising spectrum of action. They exhibit an antiviral action on representatives of the group of Herpes viridae (herpes viruses), particularly on cytomegaloviruses (CMV), particularly on the human cytomegalovirus (HCMV). They are suitable accordingly for the treatment and prophylaxis of diseases, particularly of infections with viruses, especially the abovementioned viruses, and the infectious diseases caused thereby. By a viral infection is meant hereinafter not only an infection with a virus but also a disease caused by an infection with a virus.

The compounds of the general formula (I) can, on the basis of their particular properties, be used for producing medicaments which are suitable for the prophylaxis and/or treatment of diseases, particularly viral infections.

Areas of indication which may be mentioned by way of example include the following:

1) treatment and prophylaxis of HCMV infections in AIDS patients (retinitis, pneumonitis, gastrointestinal infections).

2) Treatment and prophylaxis of cytomegalovirus infections in bone-marrow and organ transplant patients who develop often life-threatening HCMV pneumonitis, or encephalitis, and gastrointestinal and systemic HCMV infections.

3) Treatment and prophylaxis of HCMV infections in neonates and infants.

4) Treatment of an acute HCMV infection in pregnant women.

5) Treatment of HCMV infection in immunosuppressed patients in association with cancer and cancer therapy.

The compounds of the invention are preferably used for producing medicaments which are suitable for the prophylaxis and/or treatment of infections with a representative of the group of Herpes viridae, particularly a cytomegalovirus, in particular the human cytomegalovirus.

The compounds of the invention, on the basis of their pharmacological properties, can be used alone and, if required, in combination with other active ingredients, particularly active antiviral ingredients such as gancyclovir or acyclovir, for example, for the treatment and/or prevention of viral infections, especially HCMV infections.

The present invention further provides for the use of the compounds of the invention for the treatment and/or prophylaxis of diseases, preferably of viral infections, particularly of infections with the human cytomegalovirus (HCMV) or with another representative of the group of the Herpes viridae.

The present invention further provides for the use of the compounds of the invention for the treatment and/or prophylaxis of diseases, especially of the aforementioned diseases.

The present invention further provides for the use of the compounds of the invention for producing a medicament for the treatment and/or prophylaxis of diseases, especially of the aforementioned diseases.

The present invention further provides a method for the treatment and/or prophylaxis of diseases, especially of the aforementioned diseases, using an antivirally active amount of the compounds of the invention.

The compounds of the invention may act systemically and/or locally. For this purpose they may be administered in a suitable way, such as, for example, orally, parenterally, pulmonally, nasally, sublingually, lingually, buccally , rectally, dermally, transdermally, conjunctivally, optically or as an implant or stent.

For these administration routes it is possible to administer the compounds of the invention in suitable administration forms.

Administration forms suitable for oral administration are those which function according to the prior art and deliver the compounds of the invention rapidly and/or in modified form, and which comprise the compounds of the invention in crystalline and/or amorphized and/or dissolved form, such as, for example, tablets (uncoated or coated tablets, having for example coatings which are resistant to gastric juice or are insoluble or dissolve with a delay and control the release of the compound of the invention), tablets which disintegrate rapidly in the mouth, or films/wafers, films/lyophilizates, capsules (for example, hard or soft gelatin capsules), sugar-coated tablets, granules, pellets, powders, emulsions, suspensions, aerosols or solutions.

Parenteral administration can take place with avoidance of an absorption step (for example, intravenously, intraarterially, intracardiacally, intraspinally or intralumbarly) or with inclusion of absorption (for example, intramuscularly, subcutaneously, intracutaneously, percutaneously or intraperitoneally). Administration forms suitable for parenteral administration include injection preparations and infusion preparations in the form of solutions, suspensions, emulsions, lyophilizates or sterile powders.

Examples of drug forms suitable for the other administration routes include, for example, drug forms for inhalation (including powder inhalers, nebulizers), nasal drops, nasal solutions and nasal sprays; tablets, films/wafers or capsules for lingual, sublingual or buccal administration, suppositories, preparations for the eyes or ears, vaginal capsules, aqueous suspensions (lotions, shaking mixtures), lipophilic suspensions, ointments, creams, transdermal therapeutic systems, milk, pastes, foams, dusting powders, implants or stents.

The compounds of the invention can be converted into the administration forms recited. This can be done in a manner known per se by mixing with inert, nontoxic,

pharmaceutically appropriate excipients. These excipients include, among others, carriers (for example, microcrystalline cellulose, lactose, mannitol), solvents (for example, liquid polyethylene glycols), emulsifiers and dispersants or wetting agents (examples being sodium dodecyl sulfate, polyoxysorbitan oleate), binders (for example, polyvinylpyrrolidone), synthetic and natural polymers (for example, albumin), stabilizers (e.g. antioxidants such as, for example, ascorbic acid), colorants (e.g., inorganic pigments such as, for example, iron oxides) and taste- and/or odor-masking agents.

The present invention further provides medicaments which comprise at least one compound of the invention, usually together with one or more inert, nontoxic, pharmaceutically appropriate excipients, and also for their use for the purposes specified above.

In general it has proven advantageous in the case of intravenous administration to administer amounts of about 0.001 to 10 mg/kg, preferably about 0.01 to 5 mg/kg, of body weight in order to achieve effective results, and, in the case of oral administration, the dose is about 0.01 to 25 mg/kg, preferably 0.1 to 10 mg/kg, of body weight.

It may nevertheless be necessary where appropriate to deviate from the amounts specified, specifically as a function of body weight, administration route, individual response to the active ingredient, mode of preparation and time or interval at which administration takes place. Thus in certain cases it may be sufficient to employ less than the minimum amount mentioned above, while in other cases the upper limit mentioned must be exceeded. In the event of administration of relatively large amounts it may be advisable to divide them into a number of individual doses over the day.

The percentages in the tests and examples below are percentages by weight unless otherwise indicated; parts are parts by weight. Solvent ratios, dilution ratios and concentration figures of liquid/liquid solutions are based in each case on volume.

A. Examples

Abbreviations used:

CD_3CN	Deuteroacetonitrile
DCI	direct chemical ionization (in MS)
DCM	Dichloromethane
DIEA	*N,N*-diisopropylethylamine (Hünig's base)
DMSO	dimethyl sulfoxide
DMF	*N,N*-dimethylformamide
EA	ethyl acetate (acetic acid ethyl ester)
EI	electron impact ionization (in MS)
ESI	electrospray ionization (in MS)
h	Hour
HPLC	high-pressure, high-performance liquid chromatography
conc.	Concentrated
LC-MS	liquid chromatography-coupled mass spectroscopy
LDA	lithium diisopropylamide
m.p.	melting point
MS	mass spectroscopy
NMR	nuclear magnetic resonance spectroscopy
RP-HPLC	reverse phase HPLC
RT	room temperature
R_t	retention time (in HPLC)
THF	Tetrahydrofuran
TLC	thin-layer chromatography

HPLC and LC-MS methods:

Method 1 (LC-MS):

Instrument: Micromass Quattro LCZ, with HPLC Agilent series 1100; column: Grom-SIL120 ODS-4 HE, 50 mm x 2.0 mm, 3 µm; eluent A: 1 l water + 1 ml 50% formic acid, eluent B: 1 l acetonitrile + 1 ml 50% formic acid; gradient: 0.0 min 100%A → 0.2 min

100%A → 2.9 min 30%A → 3.1 min 10%A → 4.5 min 10%A; oven: 55°C; flow rate: 0.8 ml/min; UV detection: 208-400 nm.

Method 2 (LC-MS):

MS instrument type: Micromass ZQ; HPLC instrument type: Waters Alliance 2790; column: Grom-Sil 120 ODS-4 HE, 50 mm x 2 mm, 3.0 µm; eluent A: water + 500 µl 50% formic acid; eluent B: acetonitrile + 500 µl 50% formic acid/l; gradient: 0.0 min 5%B → 2.0 min 40%B → 4.5 min 90%B → 5.5 min 90%B; oven: 45°C; flow rate: 0.0 min 0.75 ml/min → 4.5 min 0.75 ml/min 5.5 min → 5.5 min 1.25 ml/min; UV detection: 210 nm.

Method 3 (LC-MS):

Instrument: Micromass Platform LCZ with HPLC Agilent series 1100; column: Grom-SIL120 ODS-4 HE, 50 mm x 2.0 mm, 3 µm; eluent A: 1 l water + 1 ml 50% formic acid, eluent B: 1 l acetonitrile + 1 ml 50% formic acid; gradient: 0.0 min 100%A → 0.2 min 100%A → 2.9 min 30%A → 3.1 min 10%A → 4.5 min 10%A; oven: 55°C; flow rate: 0.8 ml/min; UV detection: 208-400 nm.

Method 4 (LC-MS):

MS instrument type: Micromass ZQ; HPLC instrument type: HP 1100 series; UV DAD; column: Grom-Sil 120 ODS-4 HE, 50 mm x 2 mm, 3.0 µm; eluent A: water + 500 µl 50% formic acid/l, eluent B: acetonitrile + 500 µl 50% formic acid/l; gradient: 0.0 min 0%B → 2.9 min 70%B → 3.1 min 90%B → 4.5 min 90%B; oven: 50 °C; flow rate: 0.8 ml/min; UV detection: 210 nm.

Method 5 (LC-MS):

MS instrument type: Micromass ZQ; HPLC instrument type: Waters Alliance 2795; column: Merck Chromolith SpeedROD RP-18e, 50 mm x 4.6 mm; eluent A: water + 500 µl 50% formic acid/l; eluent B: acetonitrile + 500 µl 50% formic acid/l; gradient: 0.0 min 10%B→ 3.0 min 95%B→ 4.0 min 95%B; oven: 35°C; flow rate: 0.0 min 1.0 ml/min→ 3.0 min 3.0 ml/min→ 4.0 min 3.0 ml/min; UV detection: 210 nm.

Method 6 (preparative HPLC):

Column: Nucleosil 100-5 C 18 Nautilus, 5 µm, 20 mm x 50 mm, 220 nm, 550 µl injection volume; eluent A: water + 0.3% formic acid, eluent B: acetonitrile; gradient: 0.0 min 10%B, 2.0 min 10%B, 6.0 min 90%B, 7.0 min 90%B, 7.1 min 10%B, 8.0 min 10%B; flow rate: 25 ml/min; UV detection: 210 nm.

Method 7 (preparative HPLC):

Column: Waters XTerra Prep MS C18, 5 µm, 19 mm x 20 mm; injection volume 700 µl; eluent A: acetonitrile, eluent B: water + 0.1% formic acid; gradient: 0.00 min 10%A, 2.00 min 10%A, 6.00 min 90%A, 7.00 min 90%A, 7.10 min 10%A, 8.00 min 10%A; flow rate: 25 ml/min; UV detection: 220 nm.

Method 8 (LC-MS):

Instrument: Micromass TOF-MUX-Interface 4-fold parallel injection with HPLC Waters 600; column: Grom-SIL 120, 50 mm x 2.0 mm, 3.0 µm; eluent A: 1 l water + 1 ml 50% formic acid, eluent B: 1 l acetonitrile + 1 ml 50% formic acid; gradient: 0.0 min 100%A → 0.2 min 100%A → 2.9 min 30%A → 3.1 min 10%A → 4.5 min 10%A → 4.6 min 100%A → 6.5 min 100%A; oven: room temperature; flow rate: 0.8 ml/min; UV detection: 210 nm.

Method 9 (preparative HPLC):

Column: Macherey-Nagel VP 50/21 Nucleosil 100-5 C18 Nautilus, 20 mm x 50 mm; injection volume 500 µl; eluent A: acetonitrile, eluent B: water + 0.1% formic acid; gradient: 0.00 min 10%A, 2.00 min 10%A, 6.00 min 90%A, 7.00 min 90%A, 7.10 min 10%A, 8.00 min 10%A; flow rate: 25 ml/min; UV detection: 220 nm.

Method 10 (LC-MS):

Instrument: Micromass Platform LCZ with HPLC Agilent series 1100; column: Grom-SIL120 ODS-4 HE, 50 mm x 2.0 mm, 3 µm; eluent A: 1 l water + 1 ml 50% formic acid, eluent B: 1 l acetonitrile + 1 ml 50% formic acid; gradient: 0.0 min 100%A → 0.2 min 100%A → 2.9 min 30%A → 3.1 min 10%A → 4.5 min 10%A; oven: 55°C; flow rate: 0.8 ml/min; UV detection: 210 nm.

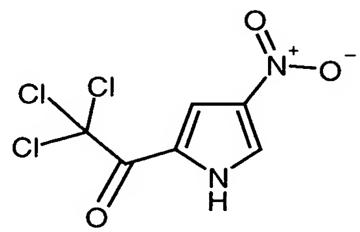
Method 11 (preparative HPLC):

Column material: YMC GEL ODS AQ S 5/15 µm; eluent: acetonitrile-water, gradient: 10:90 - > 90:10.

Starting compounds

Example 1A

2,2,2-trichloro-1-(4-nitro-1H-pyrrol-2-yl)ethanone



10 g (47 mmol) of 2,2,2-trichloro-1-(1H-pyrrol-2-yl)ethanone are dissolved in 47.2 ml of acetic anhydride. At –50 to -60°C 2.21 ml (47 mmol) of 90% strength nitric acid are added dropwise. The reaction mixture is slowly warmed to 0°C and then stirred at room temperature for 1 h. The reaction solution is diluted with ethyl acetate and washed twice with saturated sodium chloride solution and four times with saturated sodium hydrogen carbonate solution. The organic phase is dried with magnesium sulfate and concentrated by evaporation under reduced pressure. The evaporation residue is admixed with a mixture of 10 ml of diethyl ether and 20 ml of cyclohexane and left to stand at 5°C for 48 hours.

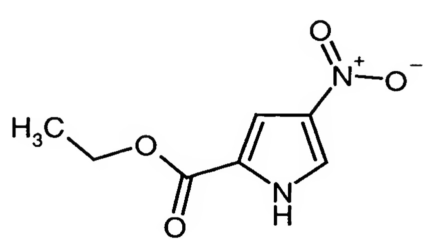
Yield: 5.2 g (43% of theory)

MS (ESI$^+$): m/z = 256 $(M+H)^+$

^{1}H-NMR (300MHz, $CDCl_3$): δ = 9.75 (broad s, 1H), 7.9 (d, 1H), 7.8 (d, 1H) ppm.

Example 2A

Ethyl 4-nitro-1H-pyrrole-2-carboxylate

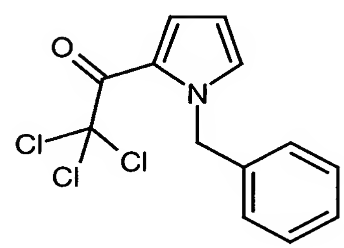


2.57 g (10 mmol) of 2,2,2-trichloro-1-(4-nitro-1H-pyrrol-2-yl)ethanone (Example 1A) are dissolved under argon in 50 ml of absolute ethanol and 1.39 ml (10 mmol) of triethylamine are added. The reaction mixture is stirred at room temperature for 16 hours. Then 100 ml of water are added dropwise and the precipitated crystals are filtered off with suction: 1 g of product. The mother liquor is concentrated under reduced pressure and the crystals which precipitate there are filtered off with suction: 0.5 g of product.

Yield: 1.5 g (71% of theory)
MS (ESI$^+$): m/z = 185 (M+H)$^+$
^{1}H-NMR (300MHz, DMSO-d_6): δ = 13.1 (broad s, 1H), 8.05 (d, 1H), 7.25 (d, 1H), 4.3 (q, 2H), 1.3 (tr, 3H) ppm.

Example 3A

1-(1-benzyl-1H-pyrrol-2-yl)-2,2,2-trichloroethanone

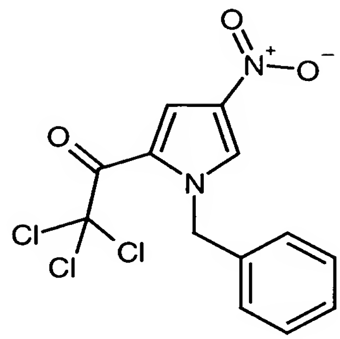


60.55 g (333.3 mmol) of trichloroacetyl chloride are dissolved in 200 ml of dichloromethane. Then a solution of 52.4 g (333.3 mmol) of 1-benzyl-1H-pyrrole in 120 ml of dichloromethane is added dropwise at room temperature over 1 hour. Argon is passed through the flask. The reaction solution is stirred overnight and then concentrated by evaporation under reduced pressure. The residue crystallizes from methanol.

Yield: 61.9 g (61% of theory)
MS (ESI$^+$): m/z = 302 (M+H)$^+$
^{1}H-NMR (200MHz, $CDCl_3$): δ = 7.6 (dd, 1H), 7.2-7.4 (m, 3H), 7.15-7.05 (m, 3H), 6.3 (dd, 1H), 5.6 (s, 2H) ppm.

Example 4A

1-(1-benzyl-4-nitro-1H-pyrrol-2-yl)-2,2,2-trichloroethanone

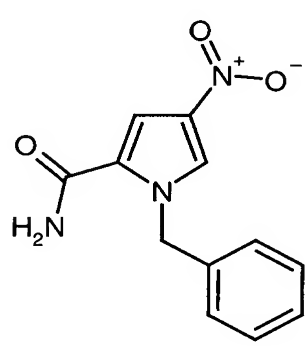


30.26 g (100 mmol) of 1-(1-benzyl-1H-pyrrol-2-yl)-2,2,2-trichloroethanone are dissolved in 100 ml of acetic anhydride, the solution is cooled to -40°C and at -40°C 10 ml (200 mmol) of 90% strength nitric acid are added dropwise. The reaction mixture is slowly warmed to room temperature and subsequently stirred for 1 hour. The reaction mixture is poured into 500 ml of ice-water and stirred vigorously for 15 minutes. The precipitate is filtered off with suction and suspended in 150 ml of methanol, with stirring, and filtered off with suction again. These crystals filtered off with suction are once again suspended in 50 ml of methanol, with stirring, filtered off with suction and dried under reduced pressure.

Yield: 25.4 g (73% of theory)
MS (ESI^+): m/z = 347 $(M+H)^+$
^{1}H-NMR (300MHz, $CDCl_3$): δ = 8.0 (d, 1H), 7.75 (d, 1H), 7.4 (m, 3H), 7.2 (m, 2H), 5.6 (s, 2H) ppm.

Example 5A

1-benzyl-4-nitro-1H-pyrrole-2-carboxamide



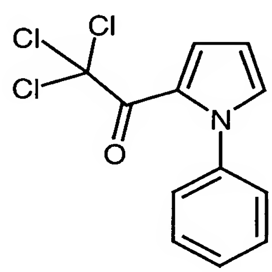
17.38 g (50 mmol) of 1-(1-benzyl-4-nitro-1H-pyrrol-2-yl)-2,2,2-trichloroethanone are dissolved in 300 ml of a saturated solution of ammonia in THF (prepared by passing 8.85 g

(520 mmol) of ammonia gas into 300 ml of THF) and the solution is stirred at room temperature for 3 hours. The reaction solution is then concentrated under reduced pressure, diethyl ether is added and the mixture is suspended with stirring.

Yield: 11.95 g (98% of theory)
MS (ESI$^+$): m/z = 246 $(M+H)^+$
^{1}H-NMR (200MHz, DMSO-d_6): δ = 8.3 (d, 1H), 7.9 (broad s, 1H), 7.5 (d, 1H), 7.4-7.15 (m, 6H), 5.7 (s, 2H) ppm.

Example 6A

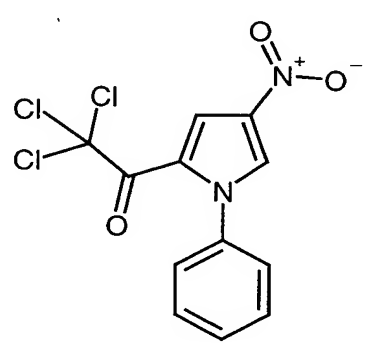
1-(1-phenyl-1H-pyrrol-2-yl)-2,2,2-trichloroethanone



Synthesis analogous to Example 3A.
Yield: 75% of theory
MS (DCI+): m/z = 288/290/292 $(M+H)^+$
^{1}H-NMR (300MHz, $CDCl_3$): δ = 7.7 (dd, 1H), 7.5 (m, 3H), 7.3 (m, 2H), 7.1 (d, 1H), 6.4 (dd, 1H).

Example 7A

1-(4-nitro-1-phenyl-1H-pyrrol-2-yl)-2,2,2-trichloroethanone



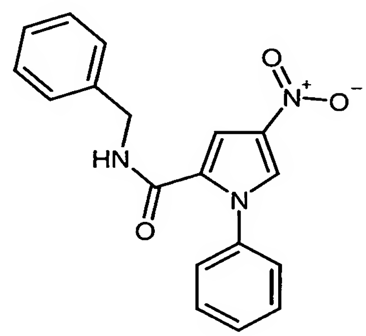
Synthesis analogous to Example 4A.

Yield: 81% of theory

^{1}H-NMR (200MHz, $CDCl_3$): δ = 8.1 (d, 1H), 7.85 (d, 1H), 7.6-7.1 (m, about 5H).

Example 8A

N-benzyl-1-phenyl-4-nitro-1H-pyrrole-2-carboxamide



Synthesis analogous to Example 5A.

Yield: 48% of theory

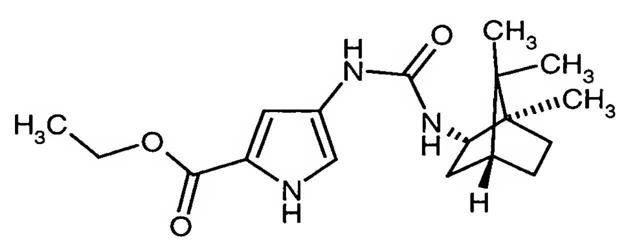
LC-MS (Method 4): R_t = 3.6 min, MS (ES+): m/z = 321 $(M+H)^+$

^{1}H-NMR (300MHz, $CDCl_3$): δ = 7.7 (d, 1H), 7.5-7.2 (m, 11H), 4.45 (d, 2H), 2.3 (m, 1H), 1.6-1.8 (m, 2H), 1.3 (m, 2H), 1.1 (m, 1H), 0.9 (s, 3H), 0.85 (s, 3H), 0.8 (s, 3H), 0.7 (dd, 1H).

Exemplary embodiments

Example 1

Ethyl 4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylate

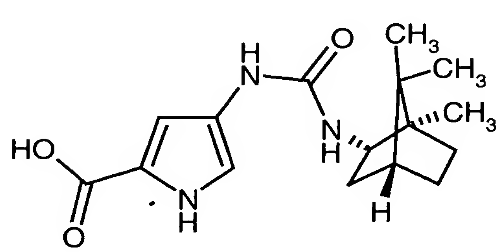


1.47 g (8 mmol) of ethyl 4-nitro-1H-pyrrole-2-carboxylate (Example 2A) are dissolved in 40 ml of THF and a spatula tip of Raney nickel and 3.2 ml (12 mmol) of 25% strength aqueous hydrazine solution are added. After 30 minutes of stirring at room temperature the solution is admixed with magnesium sulfate and filtered over kieselguhr, and the solid product is washed with ethyl acetate. The filtrate is concentrated by evaporation under reduced pressure, the residue is dissolved in 24 ml of absolute DMSO under argon, and 3.89 g (24 mmol) of N,N-carbonyldiimidazole are added. After 30 minutes of stirring at room temperature, 0.3 ml of water is added to the solution, which is stirred for 10 minutes. Then 1.23 g (8 mmol) of R-(+)-bornylamine are added and the solution is stirred for 1 h. The reaction solution is diluted with ethyl acetate and washed twice with saturated sodium chloride solution. The organic phase is washed with 1N hydrochloric acid and saturated sodium hydrogen carbonate solution, dried with magnesium sulfate and concentrated by evaporation under reduced pressure. The residue is dissolved in 15 ml of diethyl ether, and 5 ml of cyclohexane are added with stirring. The crystals are filtered off with suction and subsequently heated under reflux in diethyl ether for 1 hour. After cooling, the crystals are filtered off with suction.

Yield: 1.3 g (49% of theory)
MS (ESI$^+$): m/z = 334 $(M+H)^+$
^{1}H-NMR (300MHz, DMSO-d_6): δ = 11.4 (broad s, 1H), 7.85 (s, 1H), 7.0 (d, 1H), 6.5 (d, 1H), 6.0 (d, 1H), 4.2 (q, 2H), 3.95 (m, 1H), 2.2 (m, 1H), 1.55 – 1.8 (m, 3H), 1.35-1.1 (m 2H), 1.3 (tr, 3H), 0.9 (s, 3 H), 0.85 (s, 3H), 0.8 (d, 1H), 0.75 (s, 3H) ppm.

Example 2

4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylic acid



333 mg (1 mmol) of ethyl 4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}-carbonyl)amino]-1H-pyrrole-2-carboxylate (Example 1) are suspended in 2 ml of ethanol, and 0.24 ml (4 mmol) of 45% strength sodium hydroxide solution is added. Following the addition of 0.5 ml of water the reaction solution is left to stand at room temperature for 20 h. The reaction solution is diluted with water and washed with ethyl acetate. The aqueous phase is acidified with 1N hydrochloric acid and extracted three times with ethyl acetate. The combined extracts are dried with magnesium sulfate and concentrated by evaporation under reduced pressure. The residue crystallizes from diethyl ether.

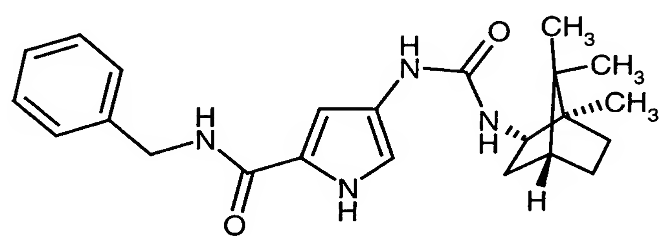
Yield: 228 mg (75% of theory)

MS (ESI$^+$): m/z = 306 $(M+H)^+$

^{1}H-NMR (200MHz, DMSO-d$_6$): δ = 12.1 (broad s, 1H), 11.4 (broad s, 1H), 7.85 (s, 1H), 7.0 (tr, 1H), 6.5 (tr, 1H), 6.0 (d, 1H), 3.95 (m, 1H), 2.2 (m, 1H), 1.55 – 1.8 (m, 3H), 1.35-1.1 (m 2H), 0.9 (s, 3 H), 0.85 (s, 3H), 0.8 (d, 1H), 0.75 (s, 3H) ppm.

Example 3

N-benzyl-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxamide



152 mg (0.5 mmol) of 4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylic acid (Example 2) are dissolved in 2 ml of DMF under argon, 243 mg (1.5 mmol) of N,N-carbonyldiimidazole are added and the mixture is stirred at room temperature for 1 h. Then 0.02 ml of water are added and stirring is carried out for 30 minutes. Following the addition of 80 mg (0.75 mmol) of benzylamine the reaction solution is left to stand at room temperature for 16 h. With stirring, first 1 ml of 1N hydrochloric acid then, slowly, a further 3 ml of water are added dropwise. The crystals are filtered off with suction.

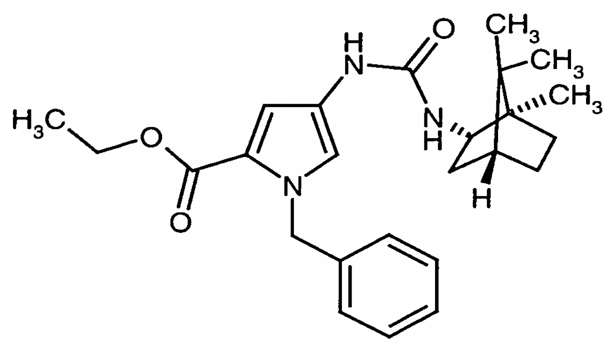
Yield: 172 mg (87% of theory)

MS (ESI$^+$): m/z = 395 (M+H)$^+$

^{1}H-NMR (300MHz, DMSO-d_6): δ = 10.95 (broad s, 1H), 8.4 (tr, 1H), 7.8 (s, 1H), 7.2-7.35 (m, 5H), 6.85 (tr, 1H), 6.6 (tr, 1H), 5.9 (d, 1H), 4.4 (d, 2H), 3.95 (m, 1H), 2.2 (m, 1H), 1.55 – 1.8 (m, 3H), 1.35-1.1 (m 2H), 0.9 (s, 3H), 0.85 (s, 3H), 0.8 (m, 1H), 0.75 (s, 3H) ppm.

Example 4

Ethyl 1-benzyl-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)-amino]-1H-pyrrole-2-carboxylate



1.67 g (5 mmol) of ethyl 4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}-carbonyl)amino]-1H-pyrrole-2-carboxylate (Example 1) are dissolved in absolute DMF, and 0.73 g (6.5 mmol) of potassium tert-butoxide is added. Stirring is continued for 5 minutes and thereafter 1.11 g (6.5 mmol) of benzyl bromide are added. After three hours of stirring at room temperature, 3 ml of water are slowly added dropwise. The crystals are filtered off with suction and washed with a 1:1 mixture of water and methanol. The crystals are recrystallized from a mixture of ethyl acetate and methanol.

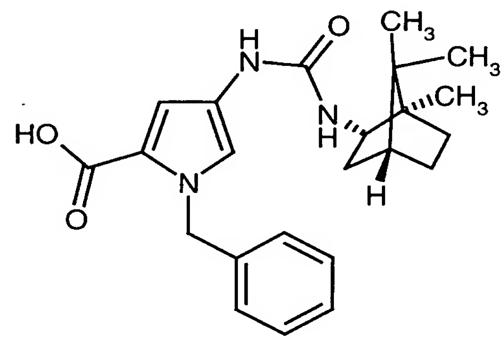
Yield: 1.2 g (57% of theory)

MS (ESI$^+$): m/z = 424 (M+H)$^+$

^{1}H-NMR (300MHz, DMSO-d_6): δ = 7.9 (s, 1H), 7.2-7.35 (m, 4H), 7.05 (d, 2H), 6.65 (d, 1H), 6.05 (d, 1H), 5.45 (d, 2H), 4.15 (q, 2H), 3.95 (m, 1H), 2.2 (m, 1H), 1.55 – 1.8 (m, 3H), 1.35-1.1 (m 2H), 1.2 (tr, 3H), 0.9 (s, 3H), 0.85 (s, 3H), 0.8 (m, 1H), 0.75 (s, 3H) ppm.

Example 5

1-benzyl-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylic acid

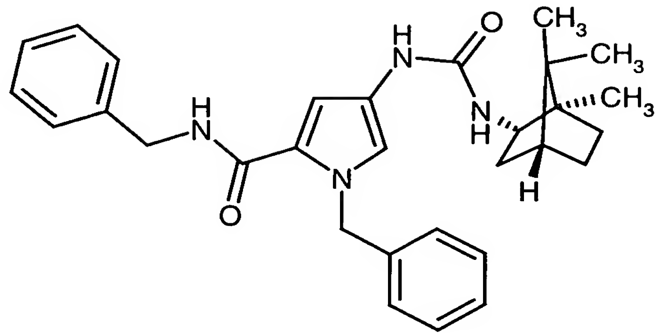


211 mg (0.5 mmol) of ethyl 1-benzyl-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylate (Example 4) are suspended in 1 ml of ethanol, and 0.24 ml (4 mmol) of 45% strength sodium hydroxide solution and 2 ml of THF are added. The reaction mixture is stirred at RT for 72 hours, diluted with water, acidified with 1N hydrochloric acid and extracted twice with ethyl acetate. After the extracts have been dried with magnesium sulfate they are concentrated by evaporation under reduced pressure.

Yield: 159 mg (80% of theory)
MS (ESI^+): m/z = 396 $(M+H)^+$
^{1}H-NMR (300MHz, DMSO-d_6): δ = 12.0 (broad s, 1H), 7.9 (s, 1H), 7.2-7.35 (m, 3H), 7.15 (d, 1H), 7.05 (d, 2H), 6.6 (tr, 1H), 6.0 (d, 1H), 5.45 (s, 2H), 3.95 (m, 1H), 2.2 (m, 1H), 1.55 – 1.8 (m, 3H), 1.35-1.1 (m 2H), 0.9 (s, 3H), 0.85 (s, 3H), 0.8 (m, 1H), 0.75 (s, 3H) ppm.

Example 6

N,1-dibenzyl-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxamide



39.5 mg (0.1 mmol) of 1-benzyl-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylic acid (Example 5) are dissolved in 0.5 ml of DMF under argon, then 48 mg (0.3 mmol) of N,N-carbonyldiimidazole are added and the mixture is stirred at room temperature for 30 minutes. Then 0.036 ml of water is added and stirring is continued for 30 minutes at RT. Then 16 mg (0.15 mmol) of benzylamine are added and the reaction solution is left to stand at RT for 24 hours. The reaction solution is filtered and purified by preparative HPLC (column: Nucleosil 100-5 C 18 Nautilus, 5 µm, 20 × 50 mm, wavelength: 220 nm, 600 µl injection volume, gradient: A = water + 0.3% formic acid, B = acetonitrile, 0 min = 10% B, 2 min = 10% B, 6 min = 90% B, 7 min = 90% B, 7.1 min = 10% B, 8 min = 10% B, flow rate 25 ml/min). Concentration of the product fractions by evaporation under reduced pressure yields 26 mg of product.

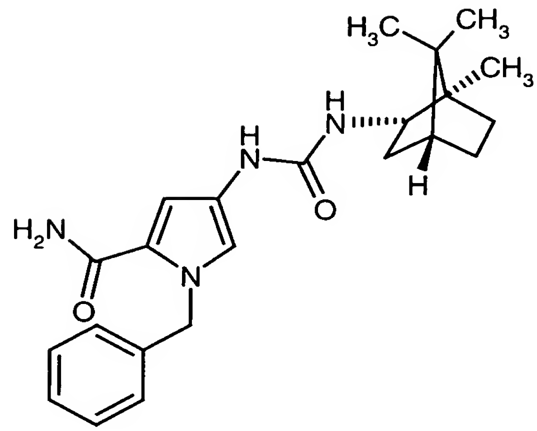
Yield: 26 mg (54% of theory)

MS (ESI$^+$): m/z = 485 (M+H)$^+$

^{1}H-NMR (200MHz, DMSO-d$_6$): δ = 8.5 (tr, 1H), 7.9 (s, 1H), 7.2-7.35 (m, 8H), 7.1-7.05 (m, 3H), 6.6 (d, 1H), 6.0 (d, 1H), 5.5 (s, 2H), 4.35 (d, 2H), 3.95 (m, 1H), 2.2 (m, 1H), 1.55 – 1.8 (m, 3H), 1.35-1.1 (m 2H), 0.9 (s, 3H), 0.85 (s, 3H), 0.8 (m, 1H), 0.75 (s, 3H) ppm.

Example 7

1-Benzyl-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxamide



1.00 g (4.1 mmol) of 1-benzyl-4-nitro-1H-pyrrole-2-carboxamide (Example 5A) is dissolved under argon protection in 20 ml of tetrahydrofuran, and then a spatula tip of Raney nickel is added. With ice cooling, 784 mg (6.1 mmol) of a 25% solution of hydrazine in water are added via a syringe. Stirring is continued for 1 h until the evolution of hydrogen is at an end. The reaction mixture is diluted with dichloromethane and filtered over kieselguhr. Washing of the solid, drying of the filtrate with magnesium sulfate, and concentration yield an oily residue. This residue is taken up in 30 ml of DMSO under argon, and 1.98 g (12.2 mmol) of 1,1'-carbonyldiimidazole are added. After 1 h of stirring at RT, two drops of water are added in order to destroy excess imidazole reagent. 625 mg (4.1 mmol) of (R)-(+)-bornylamine are added to the solution. After 3 days of stirring at RT the reaction mixture is purified by preparative HPLC separation (into 3 portions, RP18, gradient: 30% acetonitrile/70% water - > 95% acetonitrile/5% water). Concentration of the product fractions yields, after drying under reduced pressure (4 mbar, 60°C), the target product.

Yield: 813 mg (51% of theory)

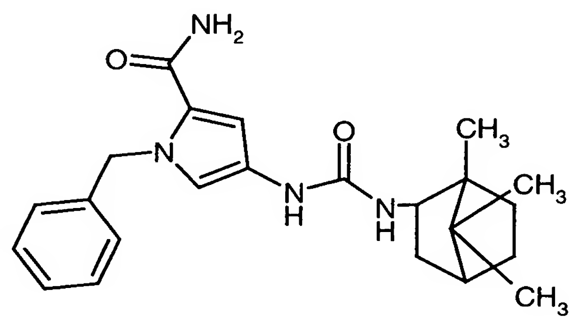
Optical rotation: $[\alpha]_{D20} = +9°$ (c = 0.28 g/100 ml, $CHCl_3$)

MS (ESI+): m/z = 395 $(M+H)^+$

^{1}H-NMR (300MHz, $CDCl_3$): δ= 7.15 – 7.35 (m, 5H), 6.85 (d, 1H), 6.5 (d, 1H), 5.95 (s, 1H), 5.3 – 5.6 (m, 4H), 4.75 (d, 1H), 4.0 (m, 1H), 2.3 (m, 1H), 1.6 – 1.8 (m, 2H), 1.3 m(2H), 1.0 (m, 1H), 0.9 (s, 3H), 0.85 (s, 3H), 0.8 (s, 3H), 0.7 (dd, 1H)

Example 8

1-benzyl-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxamide and 1-benzyl-4-[({[(1S,2R,4S)-1,7,7-trimethylbicycle[2.2.1]-hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxamide



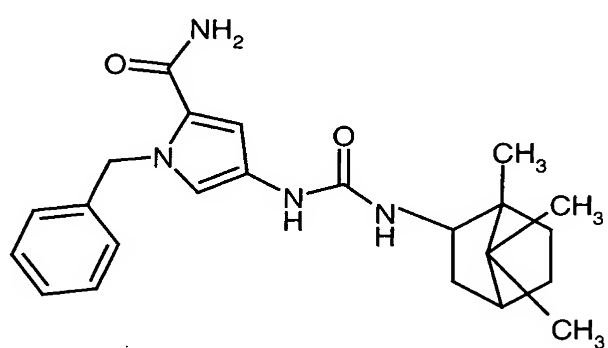
Synthesis analogous to Example 7.

Amine used: (1RS)-bornylamine (enantiomer mixture)

Yield: 55% of theory

Example 9

1-benzyl-4-[({[(1R,2R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxamide and 1-benzyl-4-[({[(1S,2S,4S)-1,7,7-trimethylbicyclo[2.2.1]-hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxamide



Synthesis analogous to Example 7.

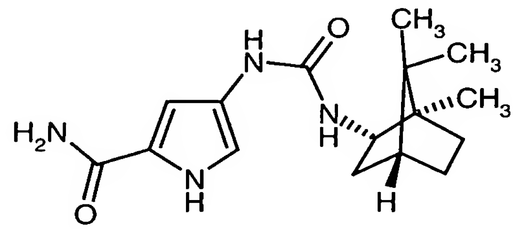
Amine used: (1RS)-isobornylamine (enantiomer mixture)

Yield: 32% of theory

m. p.: 130°C

Example 10

4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxamide

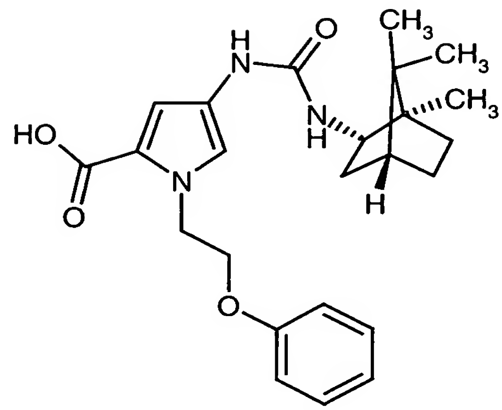


5.28 g (17.3 mmol) of 4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylic acid (Example 2) are dissolved in 69 ml of DMF under argon. Then 8.4 g (51.9 mmol) of N,N-carbonyldiimidazole are added. After 1 h of stirring at RT, 18.1 ml (242 mmol) of 25% strength aqueous ammonia solution are added dropwise with ice cooling. After 1 h of stirring at RT the reaction solution is diluted with water and extracted three times with ethyl acetate. The combined organic phases are washed twice with saturated sodium chloride solution, dried with magnesium sulfate and concentrated. The crystalline residue is stirred up with ethyl acetate and the crystals are filtered off with suction.

Yield: 3.48 g (66% of theory)

Example 11

1-(2-phenyloxyethyl)-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylic acid



1.62 g (3.56 mmol) of ethyl 1-(2-phenyloxyethyl)-4-[({[(1R,2S,4R)-1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylate (Example 27) are dissolved in 7.1 ml of ethanol and 14.3 ml of THF, and 1.7 ml (28.5 mmol) of 45% strength sodium hydroxide solution are added. The mixture is stirred at RT overnight and then diluted with 1N hydrochloric acid and extracted four times with ethyl acetate. The combined organic phases are washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated by evaporation under reduced pressure. This gives a solid foam which is used directly for the next synthesis.

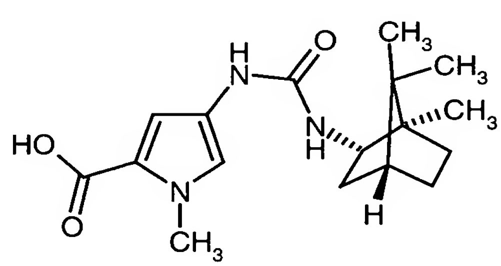
Yield: 1.75 g (quantitative)

MS (ESI^+): m/z = 426 $(M+H)^+$

^{1}H-NMR (200MHz, DMSO-d_6): δ = 7.9 (s, 1H), 7.25 (tr , 2H), 7.2 (d,1H), 6.85-6.95 (m, 3H), 6.6 (d, 1H), 6.05 (d, 1H), 4.6 (tr, 2H), 4.2 (tr, 2H), 3.95 (m, 1H), 2.2 (m, 1H), 1.55-1.8 (m, 3H), 1.35-1.1 (m 2H), 0.9 (s, 3H), 0.85 (s, 3H), 0.8 (d, 1H), 0.75 (s, 3H) ppm.

Example 12

1-methyl-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylic acid



Synthesis analogous to Example 11.

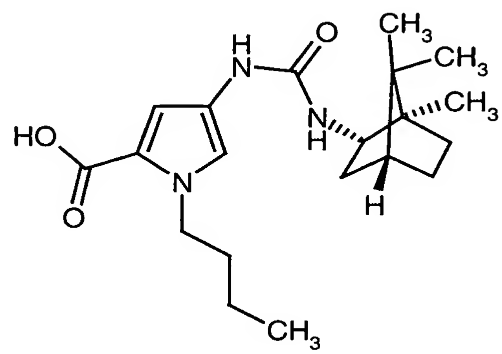
Yield: 1.16 g (quantitative)

MS (ESI$^+$): m/z = 320 $(M+H)^+$

^{1}H-NMR (200MHz, DMSO-d_6): δ = 7.9 (s, 1H), 7.05 (d,1H), 6.5 (d, 1H), 6.05 (d, 1H), 3.95 (m, 1H), 3.75 (s, 3H), 2.2 (m, 1H), 1.55-1.8 (m, 3H), 1.35-1.1 (m 2H), 0.9 (s, 3H), 0.85 (s, 3H), 0.8 (d, 1H), 0.75 (s, 3H) ppm.

Example 13

1-butyl-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylic acid



Synthesis analogous to Example 11.

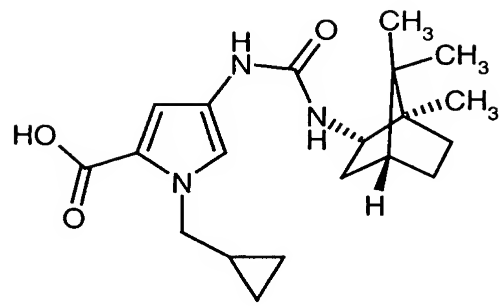
Yield: 1.09 g (quantitative)

MS (ESI$^+$): m/z = 362 $(M+H)^+$

^{1}H-NMR (300MHz, DMSO-d_6): δ = 7.85 (s, 1H), 7.1 (d,1H), 6.5 (d, 1H), 6.0 (d, 1H), 4.2 (tr, 2H), 3.95 (m, 1H), 2.2 (m, 1H), 1.55-1.8 (m, 5H), 1.35-1.1 (m, 4H), 0.9 (s, 3H), 0.85 (s, 3H), 0.8 (d, 1H), 0.75 (s, 3H) ppm.

Example 14

1-(cyclopropylmethyl)-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}-carbonyl)amino]-1H-pyrrole-2-carboxylic acid



Synthesis analogous to Example 11.

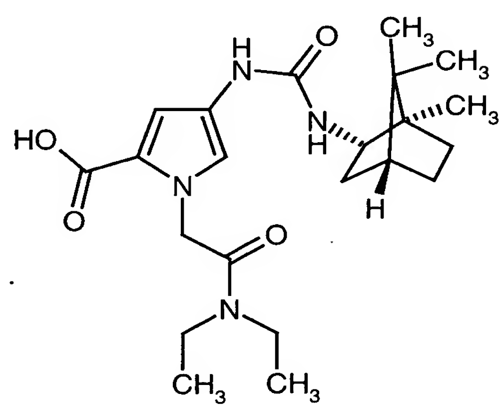
Yield: 1.66 g (quantitative)

MS (ESI$^+$): m/z = 360 (M+H)$^+$

^{1}H-NMR (300MHz, DMSO-d$_6$): δ = 7.85 (s, 1H), 7.1 (d,1H), 6.5 (d, 1H), 6.0 (d, 1H), 4.1 (dd, 2H), 3.95 (m, 1H), 2.2 (m, 1H), 1.55-1.8 (m, 3H), 1.35-1.1 (m, 3H), 0.9 (s, 3H), 0.85 (s, 3H), 0.8 (d, 1H), 0.75 (s, 3H), 0.45 (q, 2H), 0.3 (q, 2H) ppm.

Example 15

1-[2-(diethylamino)-2-oxoethyl]-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]-hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylic acid



Synthesis analogous to Example 11.

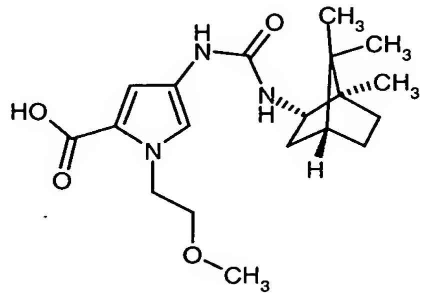
Yield: 0.72 g (quantitative)

MS (ESI$^+$): m/z = 419 (M+H)$^+$

^{1}H-NMR (300MHz, DMSO-d$_6$): δ = 7.85 (s, 1H), 7.1 (d,1H), 6.5 (d, 1H), 6.0 (d, 1H), 5.1 (s, 2H), 3.95 (m, 1H), 3.35 (q, 2H), 3.25 (q, 2H), 2.2 (m, 1H), 1.55-1.8 (m, 3H), 1.35-1.1 (m, 2H), 1.2 (tr, 3H), 1.05 (tr, 3H), 0.9 (s, 3H), 0.85 (s, 3H), 0.8 (d, 1H), 0.75 (s, 3H) ppm.

Example 16

1-(2-methoxyethyl)-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylic acid



Synthesis analogous to Example 11.

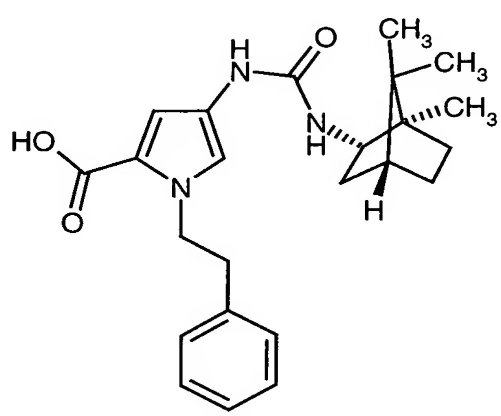
Yield: 1.1 g (quantitative)

MS (ESI$^+$): m/z = 364 $(M+H)^+$

^{1}H-NMR (300MHz, DMSO-d_6): δ = 7.85 (s, 1H), 7.1 (d,1H), 6.5 (d, 1H), 6.0 (d, 1H), 4.4 (tr, 2H), 3.95 (m, 1H), 3.55 (tr, 2H), 3.2 (s, 3H), 2.2 (m, 1H), 1.55-1.8 (m, 3H), 1.35-1.1 (m, 2H), 0.9 (s, 3H), 0.85 (s, 3H), 0.8 (d, 1H), 0.75 (s, 3H) ppm.

Example 17

1-(2-phenylethyl)-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylic acid



Synthesis analogous to Example 11.

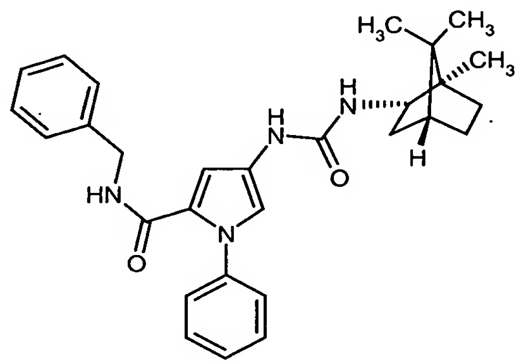
Yield: 1.64 g (quantitative)

MS (ESI$^+$): m/z = 410 $(M+H)^+$

^{1}H-NMR (200MHz, DMSO-d_6): δ = 7.85 (s, 1H), 7.15-7.35 (m, 5H), 7.1 (d,1H), 6.55 (d, 1H), 6.0 (d, 1H), 4.4 (tr, 2H), 3.95 (m, 1H), 2.9 (tr, 2H), 2.2 (m, 1H), 1.55-1.8 (m, 3H), 1.35-1.1 (m, 2H), 0.9 (s, 3H), 0.85 (s, 3H), 0.8 (d, 1H), 0.75 (s, 3H) ppm.

Example 18

N-benzyl-1-phenyl-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxamide



Synthesis analogous to Example 7 from Example 8A.

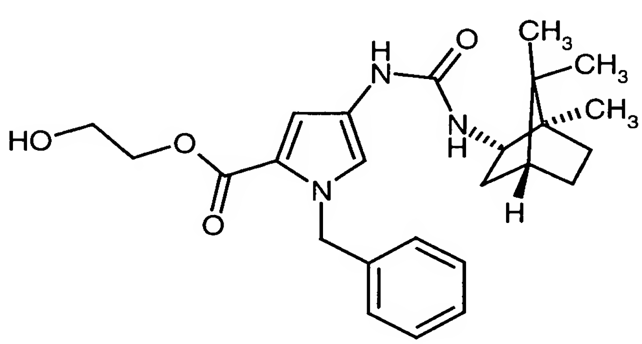
Yield: 34% of theory

LC-MS (Method 1): R_t = 4.3 min, MS (ES+): m/z = 471 $(M+H)^+$

^{1}H-NMR (300MHz, $CDCl_3$): δ = 7.15-7.45 (m, 11H), 6.60 (d, 1H), 5.95 (m, 1H), 5.35 (d, 1H), 4.40 (d, 1H), 4.1 (m, 1H), 2.3 (m, 1H), 1.6-1.8 (m, 2H), 1.3 (m, 2H), 1.1 (m, 1H), 0.9 (s, 3H), 0.85 (s, 3H), 0.8 (s, 3H), 0.7 (dd, 1H).

Example 19

2-hydroxyethyl 1-benzyl-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}-carbonyl)amino]-1H-pyrrole-2-carboxylate



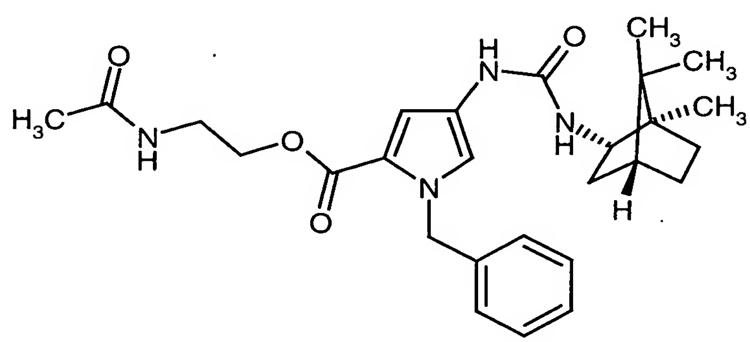
62.9 mg (0.16 mmol) of 1-benzyl-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylic acid (Example 5) are dissolved in 0.5 ml of DMF, and 77.35 mg (0.48 mmol) of N,N-carbonyldiimidazole are added. The

mixture is stirred at RT for 1 h, diluted with water and extracted twice with ethyl acetate. The combined organic phases are washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated by evaporation under reduced pressure. The evaporation residue is dissolved in 0.5 ml (9 mmol) of ethylene glycol under argon. Following the addition of 0.02 ml (0.36 mmol) of triethylamine the mixture is stirred at 100°C for 1 h. The reaction mixture is diluted with a little methanol and purified in 3 portions by preparative HPLC (Method 6). The fractions comprising product are concentrated by evaporation under reduced pressure.

Yield: 11.6 mg (17% of theory)
MS (ESI$^+$): m/z = 440 (M+H)$^+$
^{1}H-NMR (200 MHz, DMSO-d$_6$): δ = 7.95 (s, 1H), 7.2-7.4 (m, 4H), 7.1 (d, 1H), 6.7 (d, 1H), 6.1 (d, 1H), 5.5 (s, 2H), 4.85 (tr, 1H), 4.1 (tr, 2H), 3.95 (m, 1H), 3.6 (q, 2H), 2.2 (m, 1H), 1.55-1.8 (m, 3H), 1.35-1.1 (m, 2H), 0.9 (s, 3H), 0.85 (s, 3H), 0.8 (d, 1H), 0.75 (s, 3H) ppm.

<u>Example 20</u>

2-(acetylamino)ethyl-1-benzyl-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylate



59.3 mg (0.15 mmol) of 1-benzyl-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylic acid (Example 5) are dissolved in 0.5 ml of DMF under argon, and 73 mg (0.45 mmol) of N,N-carbonyldiimidazole are added. After 1 h of stirring at RT the mixture is diluted with water and extracted with ethyl acetate. The organic phase is washed with saturated sodium chloride solution, dried with magnesium sulfate and concentrated by evaporation under reduced pressure. To the evaporation residue there are added 0.2 ml of N-(2-hydroxyethyl)acetamide and 0.02 ml of

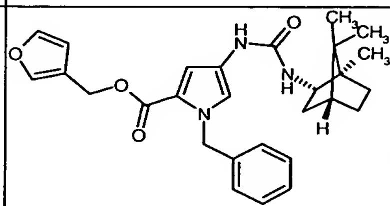
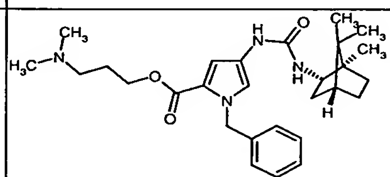
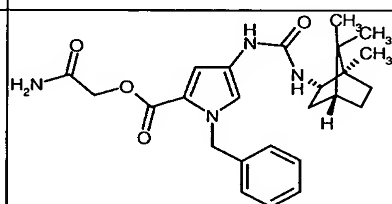
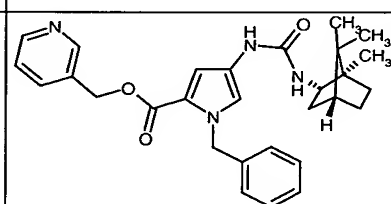
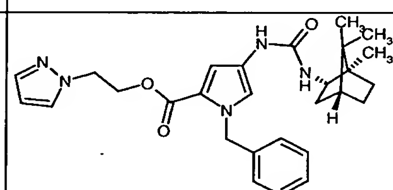
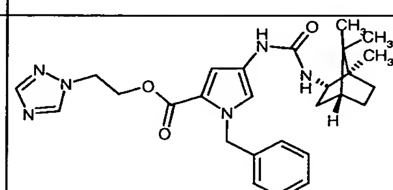
triethylamine. The reaction mixture is stirred at 100°C for 1 h, cooled, admixed with 0.4 ml of methanol, and purified by preparative HPLC (Method 6). The fractions comprising product are concentrated by evaporation under reduced pressure.

Yield: 24.1 mg (33% of theory)

MS (ESI$^+$): m/z = 481 $(M+H)^+$

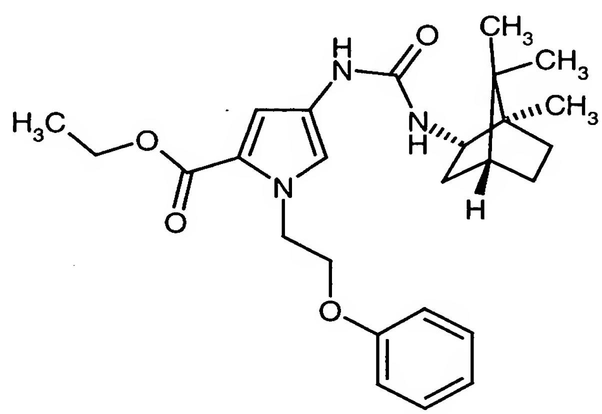
^{1}H-NMR (300MHz, DMSO-d_6): δ = 7.95 (s, 2H), 7.2-7.4 (m, 4H), 7.1 (d, 1H), 6.7 (d, 1H), 6.05 (d, 1H), 5.45 (s, 2H), 4.1 (tr, 2H), 3.95 (m, 1H), 3.3 (q, 2H), 2.2 (m, 1H), 1.8 (s, 3H), 1.55-1.8 (m, 3H), 1.35-1.1 (m, 2H), 0.9 (s, 3H), 0.85 (s, 3H), 0.8 (d, 1H), 0.75 (s, 3H) ppm.

In the same way as for Example 20 it is possible to prepare Examples 21 to 26 from the following table.

Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
21		475.58	476	3.39 (1)	5	22.3 (31)
22		480.64	481	2.4 (1)	5	9.2 (13)
23		452.55	453	2.91 (1)	5	24.2 (36)
24		486.61	487	2.97 (1)	5	21.2 (29)
25		489.62	490	3.17 (1)	5	27.9 (38)
26		490.60	491	3.01 (1)	5	27.3 (37)

Example 27

Ethyl 1-(2-phenyloxyethyl)-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylate



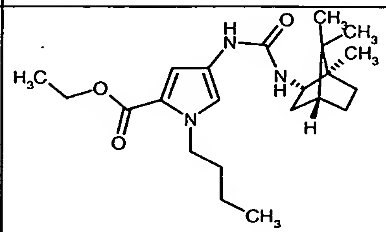
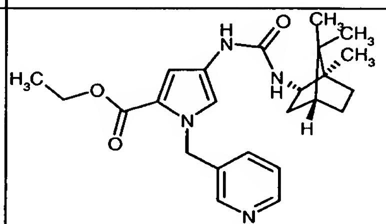
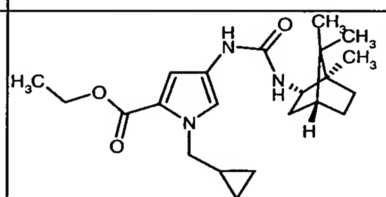
1.67 g (5 mmol) of ethyl 4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}-carbonyl)amino]-1H-pyrrole-2-carboxylate (Example 1) are dissolved in 10 ml of absolute DMF, and 1.07 g (9.5 mmol) of potassium tert-butoxide are added. After 5 minutes of stirring at RT, 1.91 g (9.5 mmol) of 1-bromoethyl 2-phenyl ether are added. The reaction mixture is stirred at RT overnight and then a further 600 mg (3 mmol) of 1-bromoethyl 2-phenyl ether and 336 mg (3 mmol) of potassium tert-butoxide are added. The reaction mixture is stirred at RT overnight and then slowly 3.5 ml of water and 0.5 ml of methanol are added dropwise. The crystals which form are filtered off with suction and washed with water/methanol (1:1 mixture) and a little methanol.

Yield: 1.87 g (83% of theory)

MS (ESI$^+$): m/z = 454 (M+H)$^+$

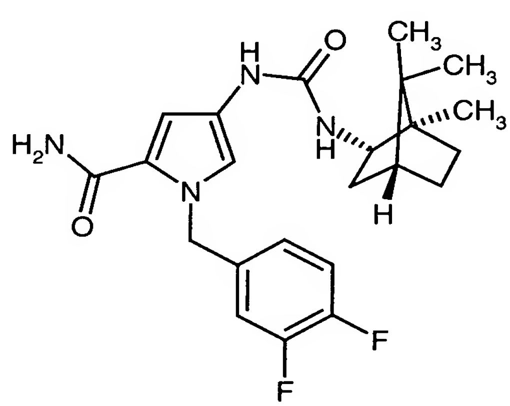
^{1}H-NMR (300MHz, DMSO-d$_6$): δ = 7.9 (s, 1H), 7.25 (tr, 2H), 7.2 (d,1H), 6.85-6.95 (m, 3H), 6.65 (d, 1H), 6.0 (d, 1H), 4.6 (tr, 2H), 4.15-4.25 (m, 4H), 3.95 (m, 1H), 2.2 (m, 1H), 1.55-1.8 (m, 3H), 1.35-1.1 (m, 2H), 1.25 (tr, 3H), 0.9 (s, 3H), 0.85 (s, 3H), 0.8 (d, 1H), 0.75 (s, 3H) ppm.

In the same way as for Example 27 it is possible to prepare Examples 28 to 30 from the following table.

Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] Yield [% of theory]
28		389.54	390	4.1 (4)	1	1.17 (60)
29		424.54	425	2.6 (1)	1	36.8 (43)
30		387.52	388	4.05 (4)	1	1.67 (86)

Example 31

1-(3,4-difluorobenzyl)-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}-carbonyl)amino]-1H-pyrrole-2-carboxamide



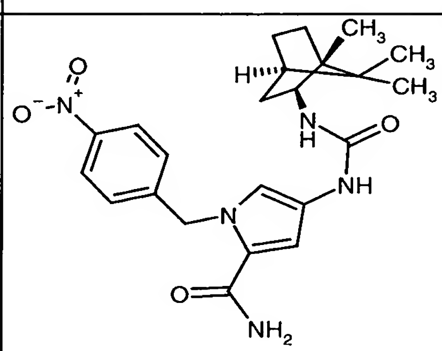
60.9 mg (0.2 mmol) of 4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxamide (Example 10) are dissolved in 0.5 ml of DMF under argon, and 8.8 mg (0.22 mmol) of sodium hydride (in 60% form) are added. After 1 h of stirring at RT, the reaction solution is added under argon to a solution of 45.5 mg (0.22 mmol) of 3,4-difluorobenzyl bromide in 0.2 ml of DMF and shaken at RT overnight. Following filtration the reaction mixture is purified by preparative HPLC (Method 7). The fractions comprising product are concentrated by evaporation under reduced pressure.

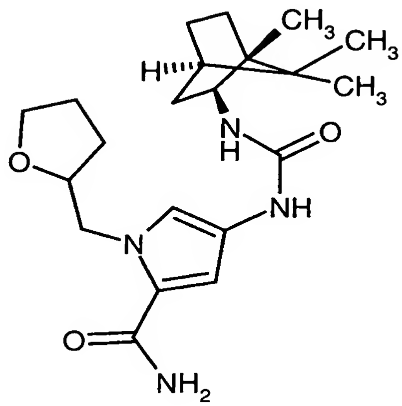
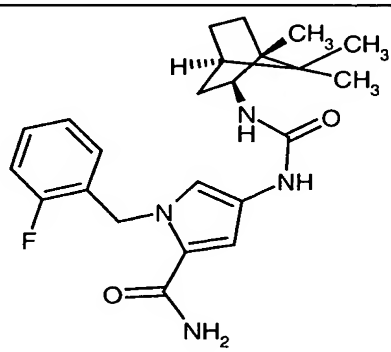
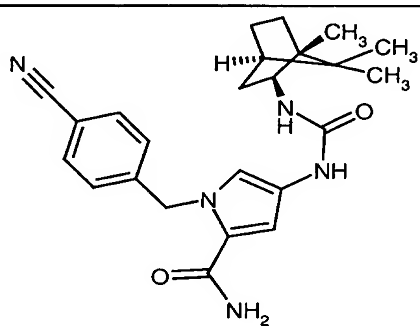
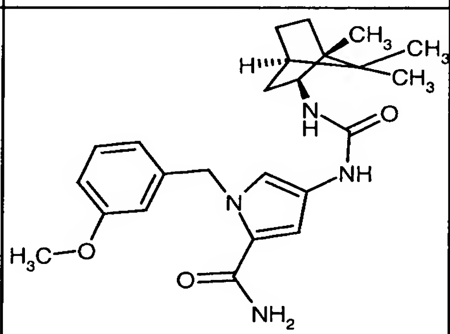
Yield: 25 mg (29% of theory)

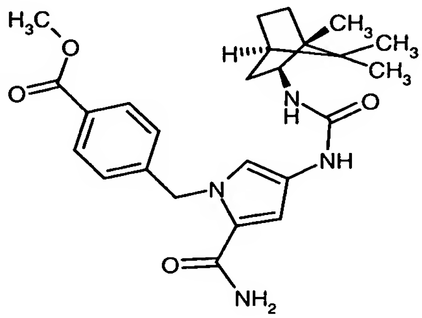
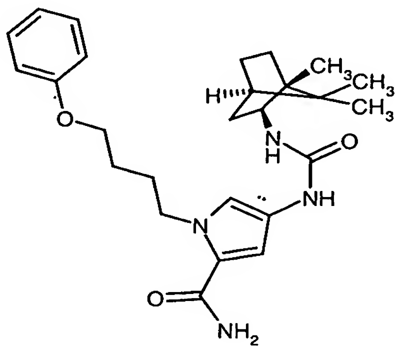
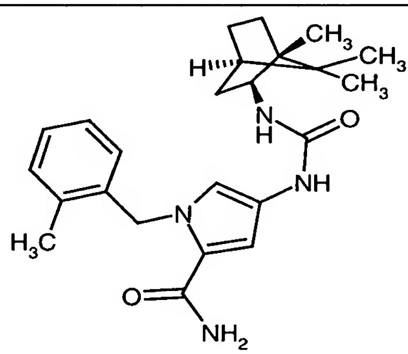
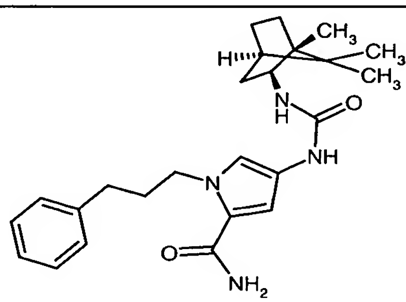
MS (ESI$^+$): m/z = 431 $(M+H)^+$

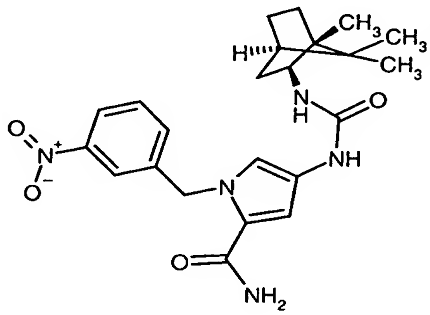
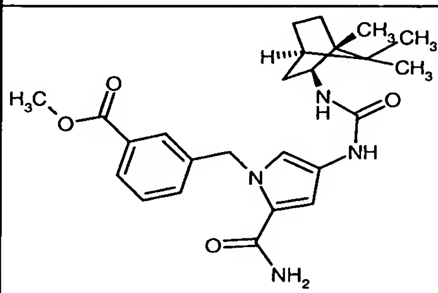
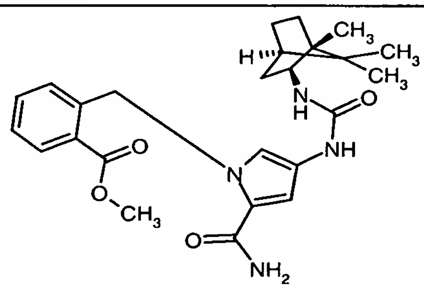
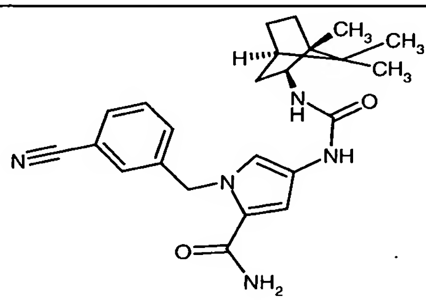
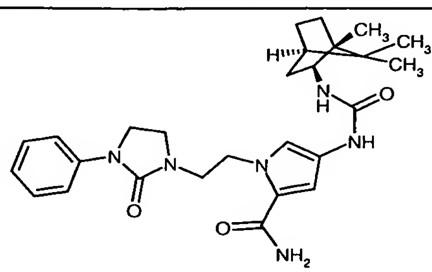
^{1}H-NMR (400MHz, DMSO-d$_6$): δ = 7.9 (s, 1H), 7.5 (broad s, 1H), 7.35 (q, 1H), 7.15 (ddd, 1H), 7.1 (d, 1H), 6.95 (m, 1H), 6.8 (broad s, 1H), 6.6 (d, 1H), 6.0 (d, 1H), 5.5 (s, 1H), 3.95 (m, 1H), 2.2 (m, 1H), 1.7 (m, 1H), 1.6 (m, 2H), 1.3 (m, 1H), 1.15 (m, 1H), 0.9 (s, 3H), 0.85 (s, 3H), 0.8 (d, 1H), 0.75 (s, 3H) ppm.

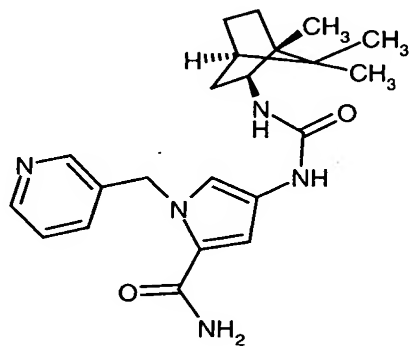
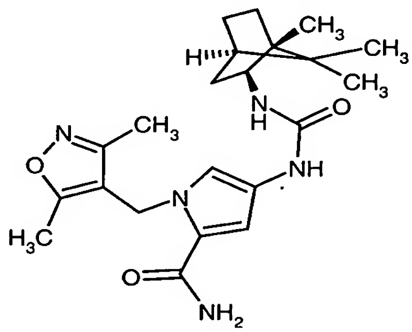
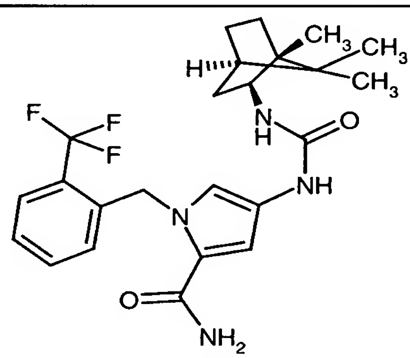
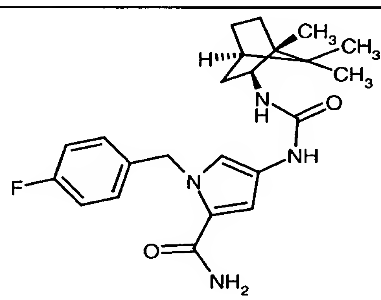
In the same way as for Example 31 it is possible to prepare Examples 32 to 59 from the following table.

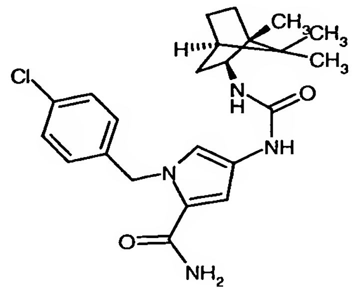
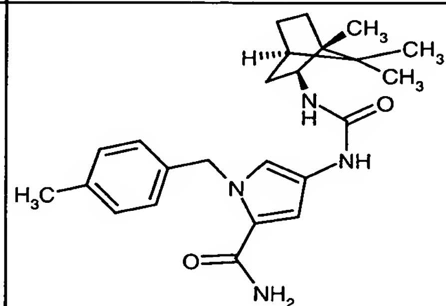
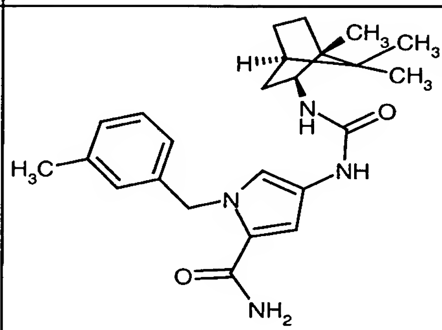
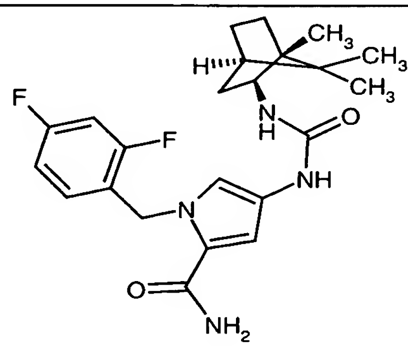
Ex. No.	**Structure**	**Molar mass**	**MS (EI): $(M+H)^+$**	**Retention time [min] (Method)**	**Reactant Ex. No.**	**Amount [mg] (Yield [% of theory])**
32		439.51	440	2.94 (1)	10	18 (20)

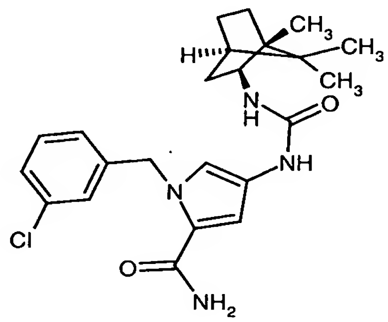
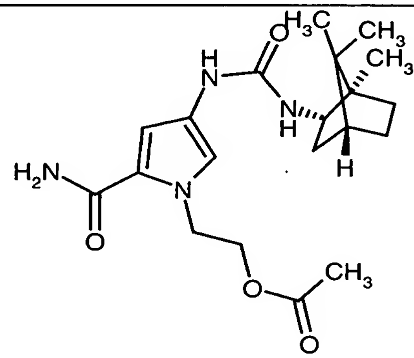
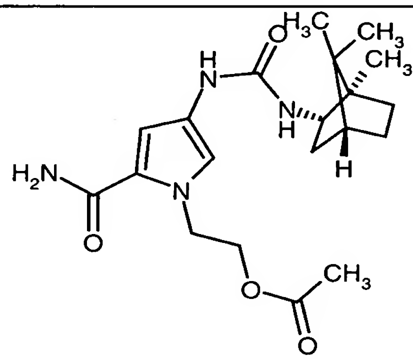
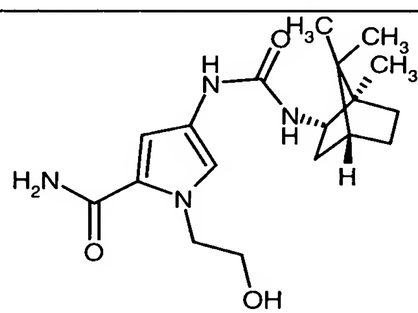
Ex. No.	Structure	Molar mass	MS (EI): (M+H)+	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
33		388.51	389	2.66 (1)	10	5 (6)
34		412.51	413	2.96 (1)	10	29 (35)
35		419.53	420	2.86 (1)	10	27 (32)
36		424.54	425	2.93 (1)	10	25 (29)

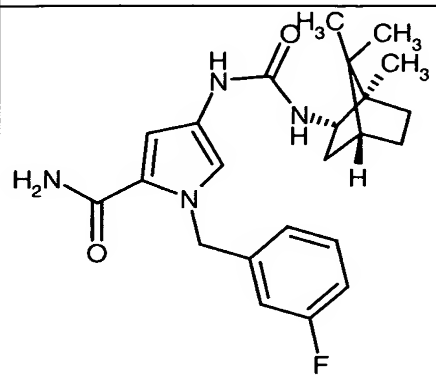
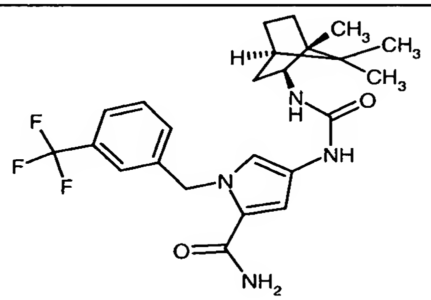
Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
37		452.55	453	2.9 (1)	10	33 (36)
38		452.60	453	3.15 (1)	10	40 (44)
39		408.54	409	3.02 (1)	10	28 (34)
40		422.57	423	3.19 (1)	10	25 (30)

Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
41		439.51	440	3.02 (1)	10	21 (24)
42		452.55	453	3 (1)	10	22 (24)
43		452.55	453	3.05 (1)	10	1.1 (1)
44		419.53	420	2.94 (1)	10	19 (23)
45		492.62	493	2.94 (1)	10	1.6 (2)

Ex. No.	Structure	Molar mass	MS (EI): (M+H)+	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
46		395.50	396	2.14 (1)	10	12 (15)
47		413.52	414	2.77 (1)	10	15 (18)
48		462.51	463	3.22 (1)	10	43 (46)
49		412.51	413	3.82 (8)	10	18 (22)

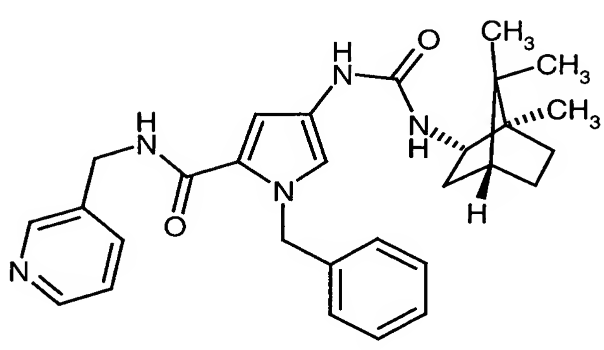
Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
50		428.96	429	3.95 (8)	10	20 (23)
51		408.54	409	3.88 (8)	10	16 (20)
52		408.54	409	3.98 (8)	10	18 (22)
53		430.50	431	3.87 (8)	10	20 (23)

Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
54		428.96	429	3.94 (8)	10	19 (22)
55		462.51	463	4 (8)	10	24 (26)
56		390.48	391	3.3 (3)	10	14.8 (49)
57		348.44	349	2.57 (4)	10	

Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
58		412.51	413	2.15 (5)	10	5.9 (7)
59		462.51	463	2.41 (5)	10	7.7 (6)

Example 60

1-benzyl-N-(pyridin-3-ylmethyl)-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxamide

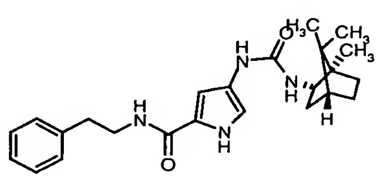
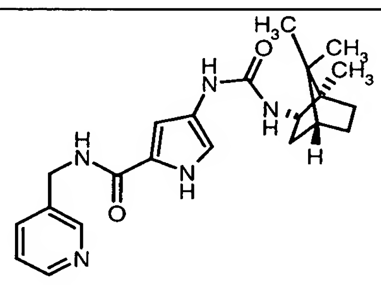
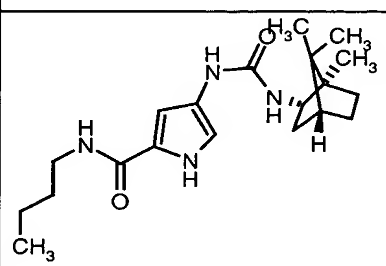


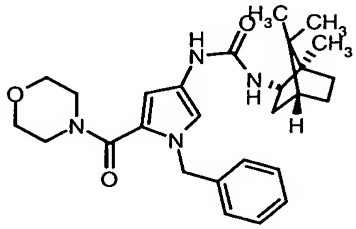
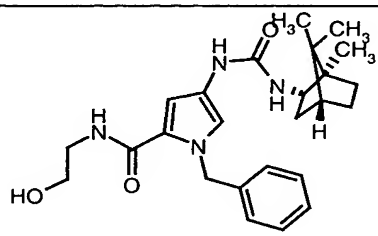
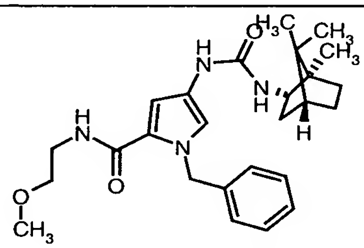
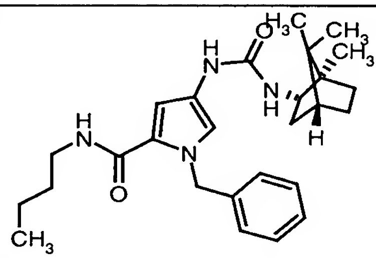
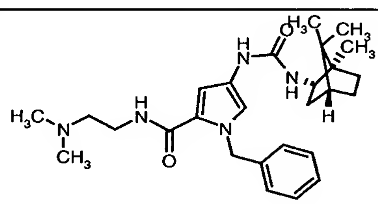
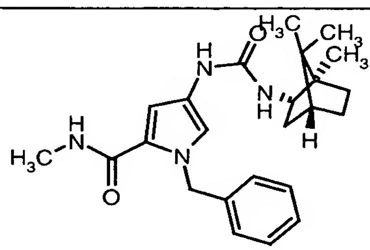
39.5 mg (0.1 mmol) of 1-benzyl-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylic acid (Example 5) are dissolved together with 48.6 mg (0.3 mmol) of N,N-carbonyldiimidazole in 0.4 ml of DMF and the

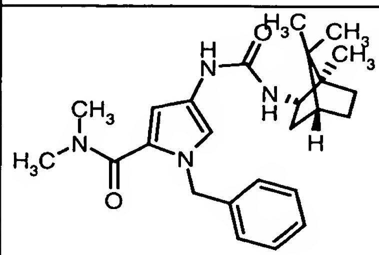
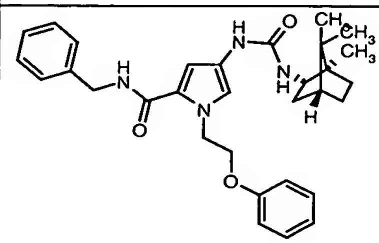
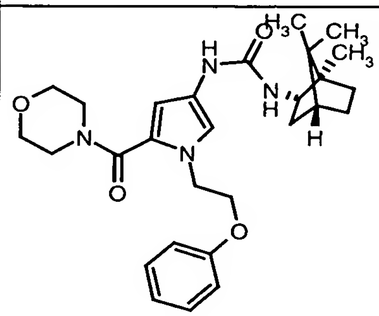
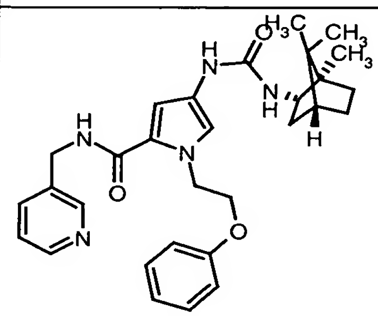
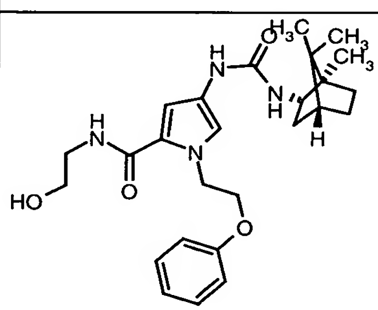
solution is left to stand at RT for 1 h. Then 0.0036 ml of water is added to the reaction solution, which is shaken for 30 minutes. Following the addition of 16.2 mg (0.15 mmol) of 3-picolylamine it is shaken at RT overnight. Following filtration, the reaction solution is purified by preparative HPLC (Method 9). The fractions comprising product are concentrated by evaporation under reduced pressure.

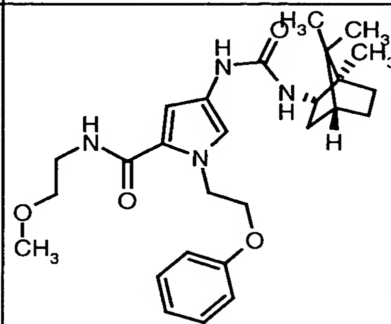
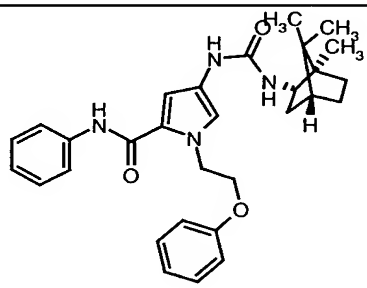
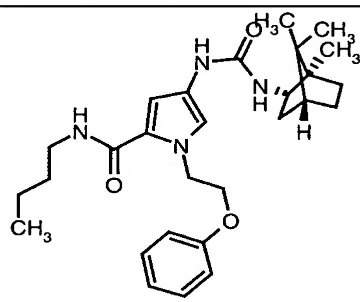
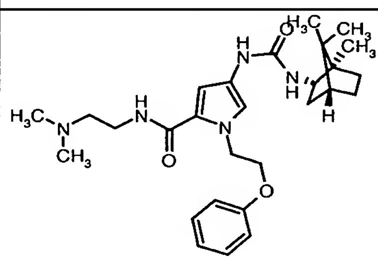
Yield: 21 mg (43% of theory)
MS (ESI$^+$): m/z = 486 (M+H)$^+$
^{1}H-NMR (200MHz, DMSO-d$_6$): δ = 8.55 (tr, 1H), 8.45 (d, 1H), 8.4 (dd, 1H), 7.9 (s, 1H), 7.6 (d tr, 1H), 7.35-7.2 (m, 4H), 7.05-7.15 (m, 3H), 6.65 (d, 1H), 6.0 (d, 1H), 5.5 (s, 1H), 4.4 (d, 2H), 3.95 (m, 1H), 2.2 (m, 1H), 1.55-1.8 (m, 3H), 1.35-1.1 (m 2H), 1.25 (tr, 3H), 0.9 (s, 3H), 0.85 (s, 3H), 0.8 (d, 1H), 0.75 (s, 3H) ppm.

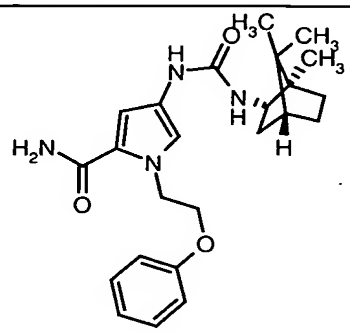
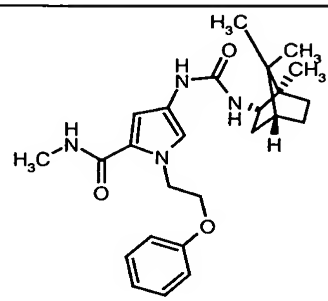
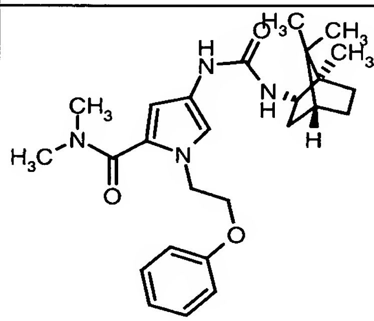
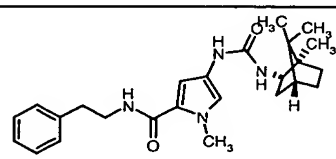
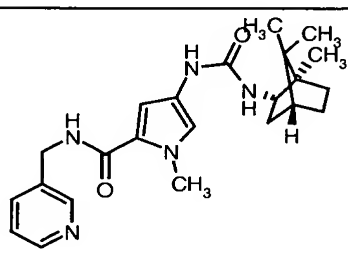
In the same way as for Example 60 it is possible to prepare Examples 61 to 150 from the following table.

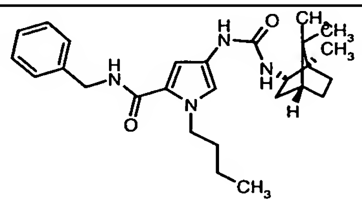
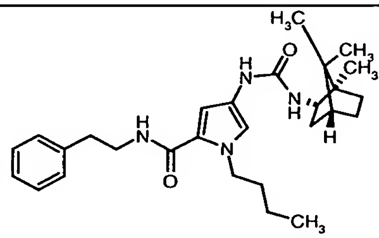
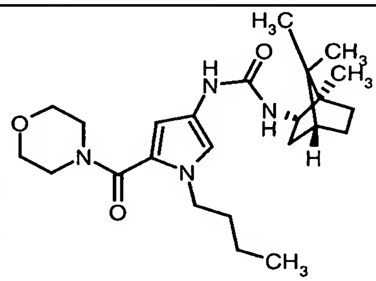
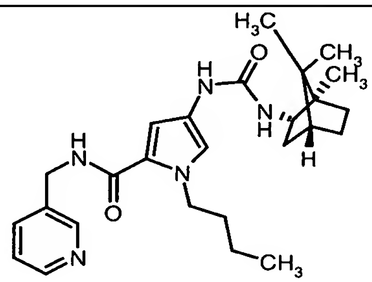
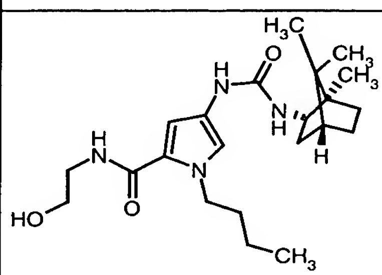
Ex. No.	Structure	Molar mass	MS (EI): (M+H)$^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
61		408.54	409	3 (1)	2	27 (66)
62		395.50	396	2.22 (1)	2	24 (60)
63		360.50	361	2.89 (1)	2	15 (41)

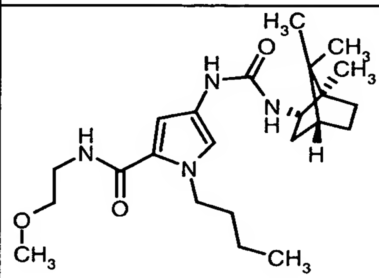
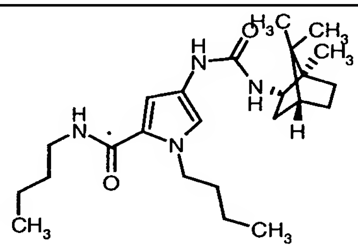
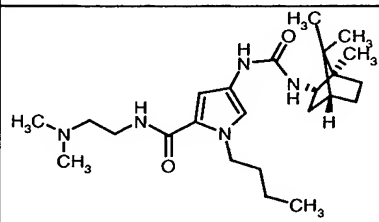
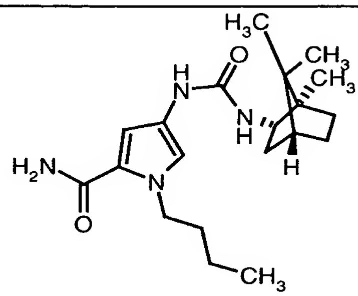
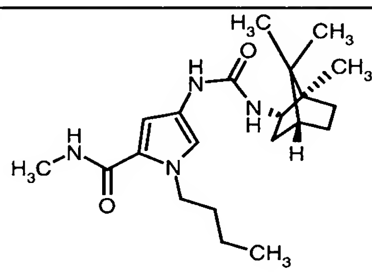
Ex. No.	Structure	Molar mass	MS (EI): (M+H)$^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
64		464.61	465	3.05 (1)	5	16 (34)
65		438.57	439	2.9 (1)	5	32 (73)
66		452.60	453	3.08 (1)	5	29 (64)
67		450.62	451	3.33 (1)	5	31 (69)
68		465.64	466	2.43 (1)	5	33 (71)
69		408.54	409	3.04 (1)	5	34 (83)

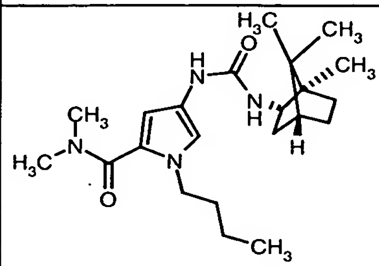
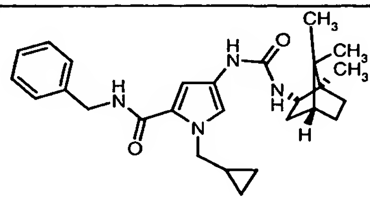
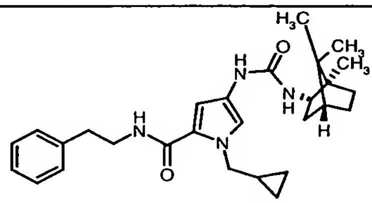
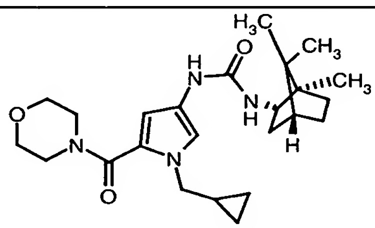
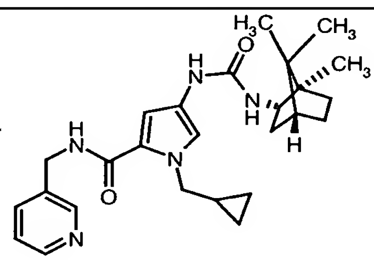
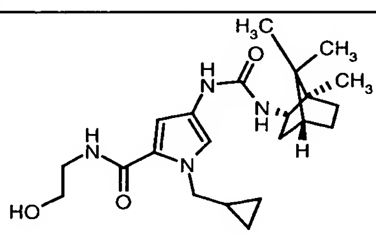
Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
70		422.57	423	3.07 (1)	5	1.8 (4)
71		514.67	515	3.39 (1)	7A	36 (70)
72		494.63	495	3.1 (1)	7A	16 (32)
73		515.65	516	2.7 (1)	7A	36 (70)
74		468.59	469	2.97 (1)	7A	29 (62)

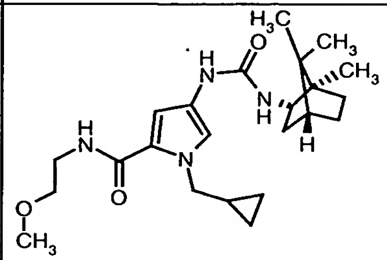
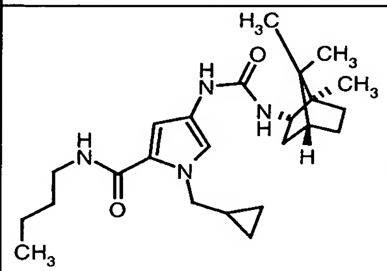
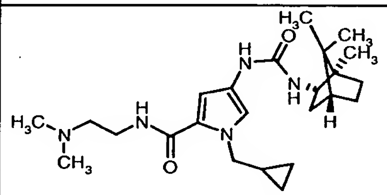
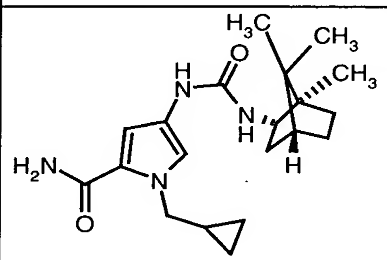
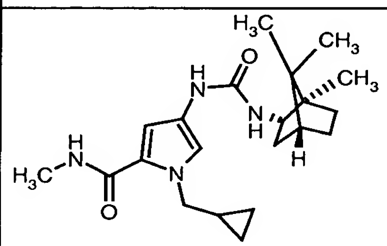
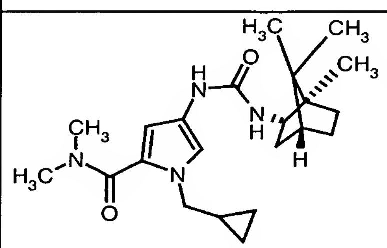
Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
75		482.62	483	3.14 (1)	7A	35 (73)
76		500.64	501		7A	
77		480.65	481	3.38 (1)	7A	34 (71)
78		495.66	496	2.5 (1)	7A	36 (73)

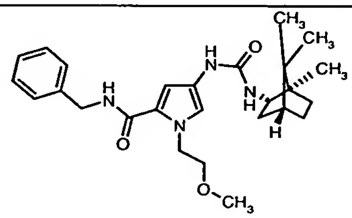
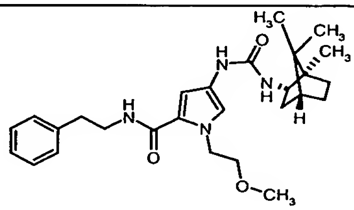
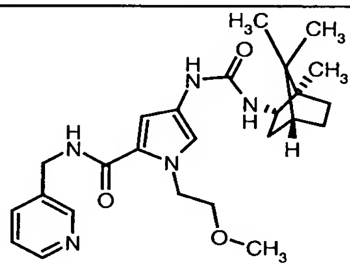
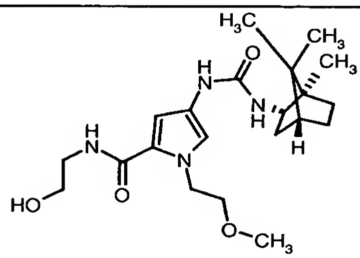
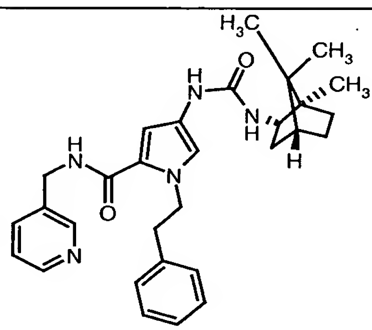
Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
79		424.54	425	3.03 (1)	7A	28 (66)
80		438.57	439	3.1 (1)	7A	30 (68)
81		452.60	453	3.12 (1)	7A	3.5 (8)
82		422.57	423	3.13 (1)	8A	28 (66)
83		409.53	410	2.31 (1)	8A	27 (66)

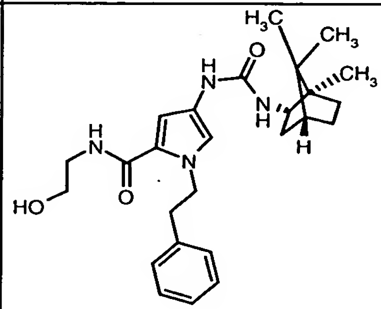
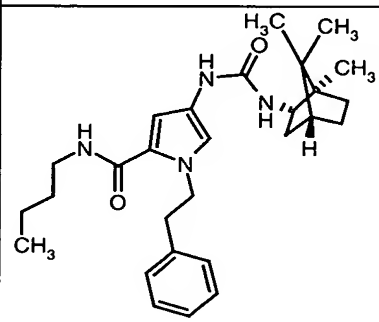
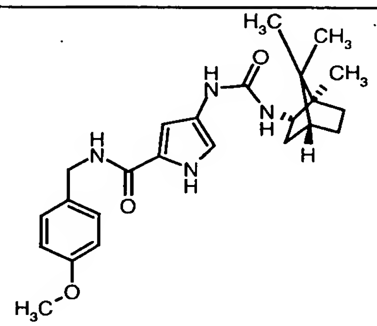
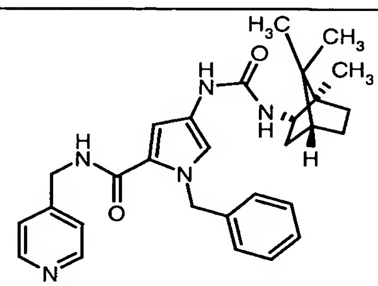
Ex. No.	Structure	Molar mass	MS (EI): (M+H)+	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
84		450.62	451	3.35 (1)	9A	32 (71)
85		464.65	465	3.4 (1)	9A	35 (75)
86		430.59	431	3.03 (1)	9A	13 (30)
87		451.61	452	2.6 (1)	9A	28 (62)
88		404.55	405	2.88 (1)	9A	25 (62)

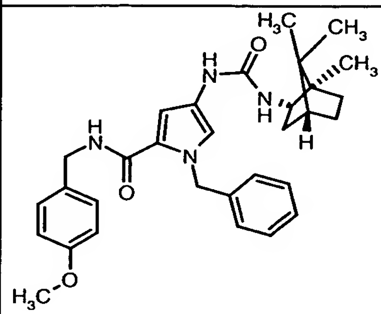
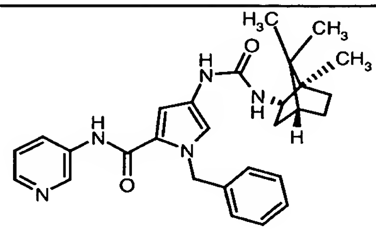
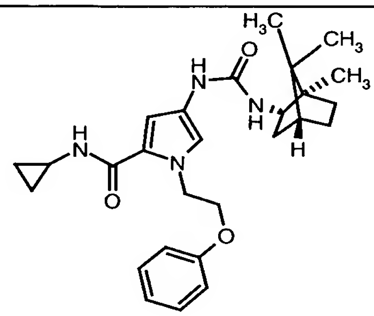
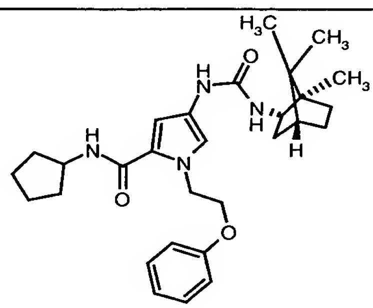
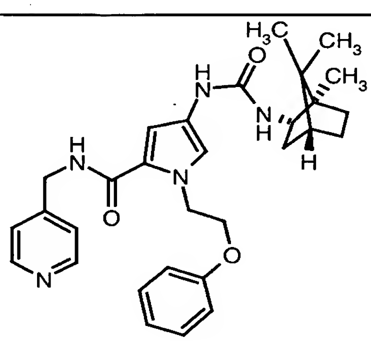
Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
89		418.58	419	3.06 (1)	9A	9.8 (23)
90		416.61	417	3.34 (1)	9A	32 (77)
91		431.62	432	2.43 (1)	9A	23 (53)
92		360.50	361	2.94 (1)	9A	25 (69)
93		374.53	375	3.01 (1)	9A	6.1 (16)

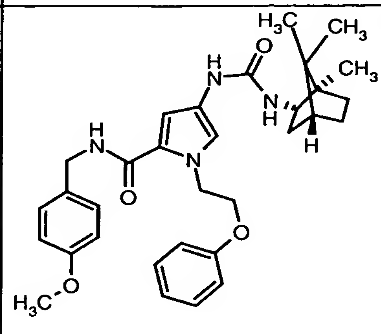
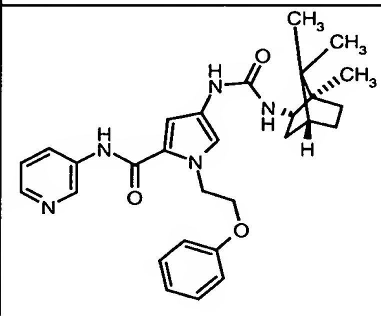
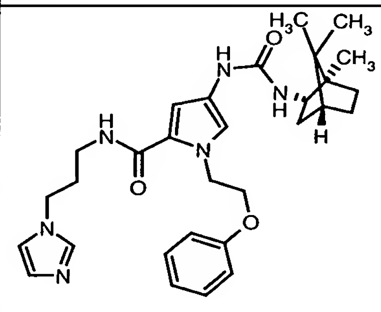
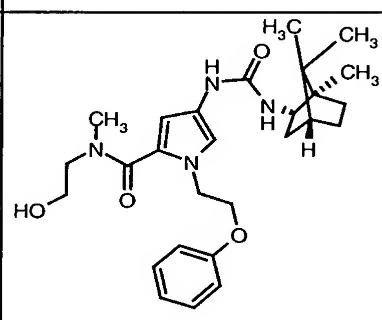
Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
94		388.55	389	3.06 (1)	9A	6.8 (18)
95		448.61	449	3.27 (1)	10A	26 (58)
96		462.63	463	3.32 (1)	10A	30 (65)
97		428.57	429	2.94 (1)	10A	3.9 (9)
98		449.60	450	2.52 (1)	10A	28 (62)
99		402.54	403	2.79 (1)	10A	16 (40)

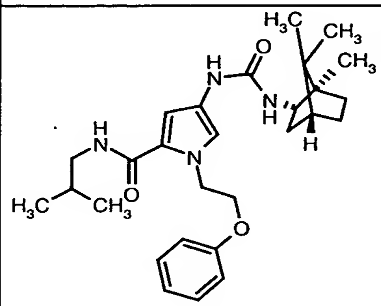
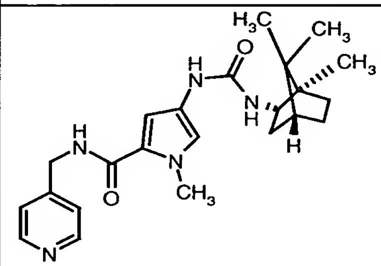
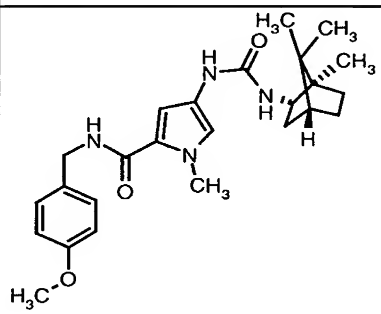
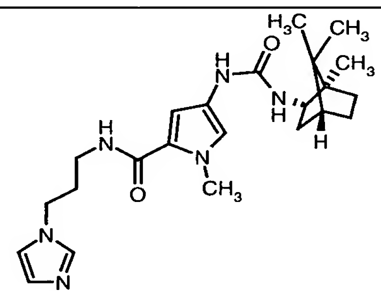
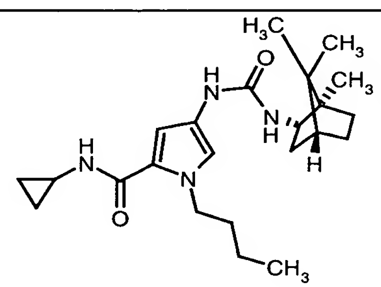
Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
100		416.56	417	2.97 (1)	10A	27 (65)
101		414.59	415	3.25 (1)	10A	26 (63)
102		429.61	430	2.33 (1)	10A	31 (72)
103		358.48	359	2.85 (1)	10A	27 (75)
104		372.51	373	2.92 (1)	10A	6.3 (17)
105		386.54	387	2.97 (1)	10A	4.7 (12)

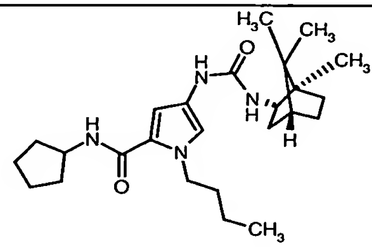
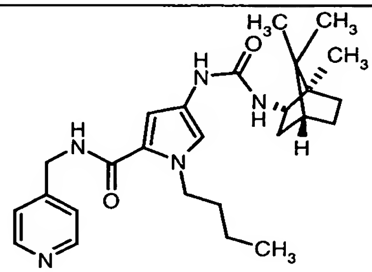
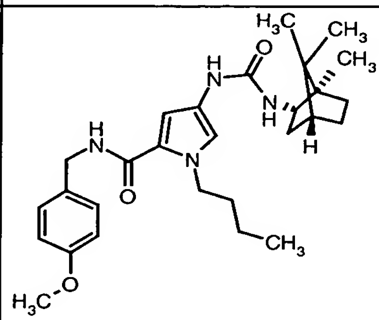
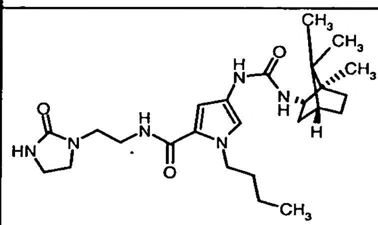
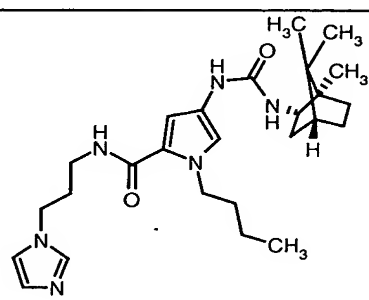
Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
106		452.60	453	3.1 (1)	12A	34 (75)
107		466.62	467	3.16 (1)	12A	35 (75)
108		453.58	454	2.36 (1)	12A	35 (77)
109		406.52	407	2.63 (1)	12A	14 (34)
110		499.66	500	2.71 (1)	13A	38 (76)

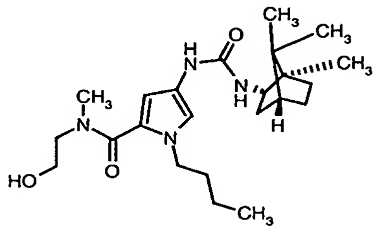
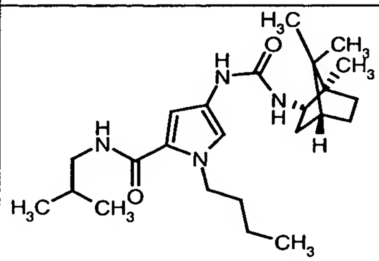
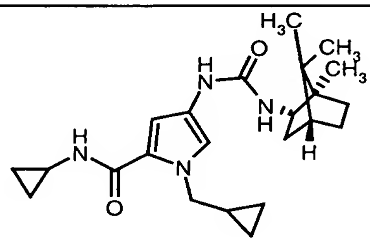
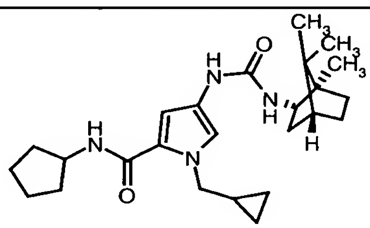
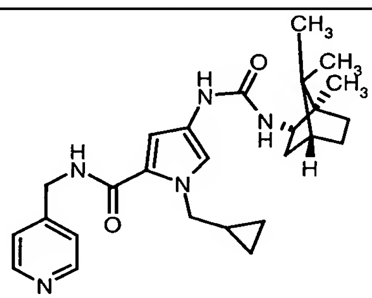
Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
111		452.60	453	2.98 (1)	13A	32 (71)
112		464.65	465	3.41 (1)	13A	38 (82)
113		424.54	425	3.04 (4)		23 (54)
114		485.63	486	2.56 (4)	5	30 (62)

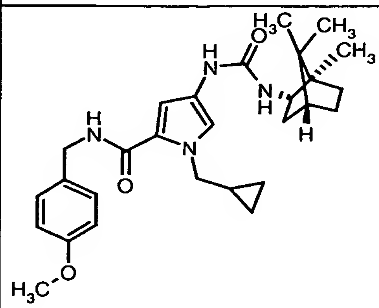
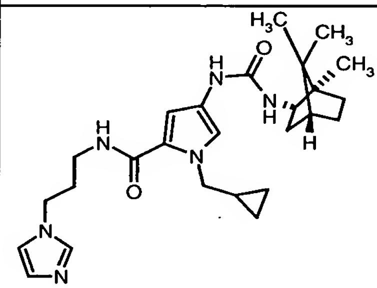
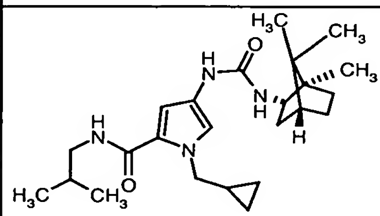
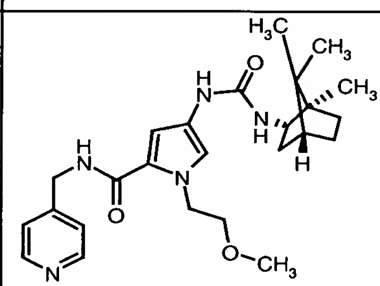
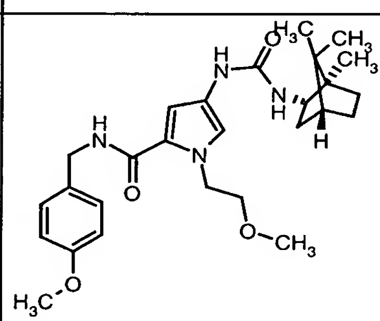
Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
115		514.67	515	3.58 (4)	5	30 (58)
116		471.60	472		5	23.2 (49)
117		464.61	465	3.43 (4)	7A	33 (71)
118		492.66	493	3.65 (4)	7A	35 (71)
119		515.65	516	2.65 (4)	7A	32 (62)

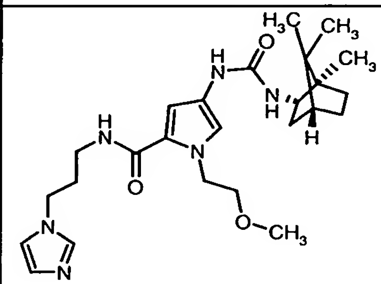
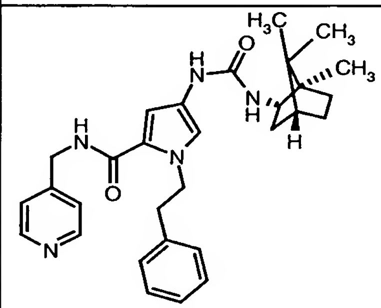
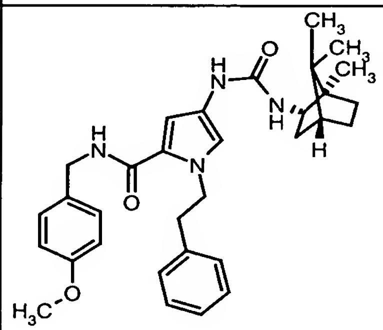
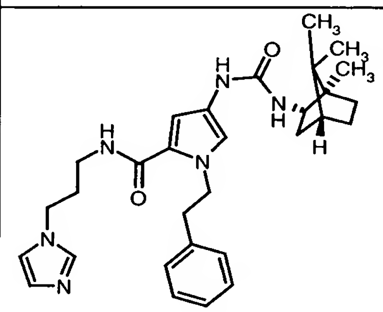
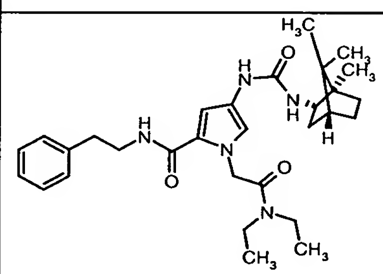
Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
120		544.69	545	3.62 (4)	7A	28 (51)
121		501.63	502		7A	20.1 (40)
122		532.69	533	2.49 (4)	7A	36 (68)
123		482.62	483	3.09 (4)	7A	27 (56)

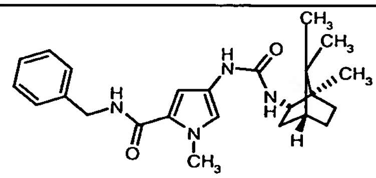
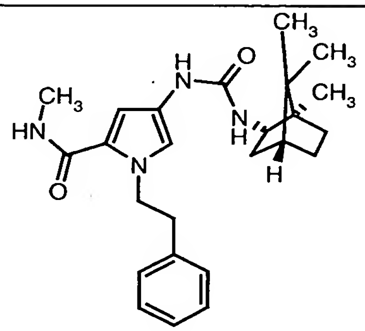
Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
124		480.65	481	3.63 (4)	7A	34 (71)
125		409.53	410	2.23 (4)	8A	20 (49)
126		438.57	439	3.21 (4)	8A	28 (64)
127		426.56	427	2.15 (4)	8A	23 (54)
128		400.56	401	3.32 (4)	9A	26 (65)

Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
129		428.62	429	3.61 (4)	9A	29 (68)
130		451.61	452	2.54 (4)	9A	25 (55)
131		480.65	481	3.59 (4)	9A	30 (62)
132		472.63	473	2.94 (4)	9A	26 (55)
133		468.64	469	2.4 (4)	9A	24 (51)

Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
134		418.58	419	2.95 (4)	9A	14 (33)
135		416.61	417	3.58 (4)	9A	16 (38)
136		398.55	399	3.2 (4)	10A	25 (63)
137		426.60	427	3.52 (4)	10A	24 (56)
138		449.60	450	2.45 (4)	10A	27 (60)

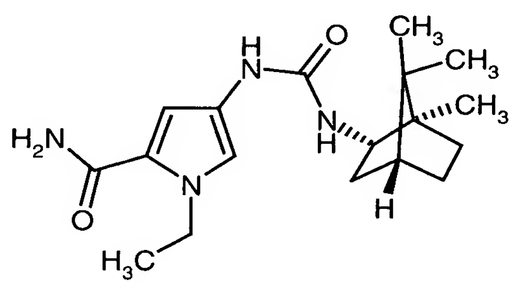
Ex. No.	Structure	Molar mass	MS (EI): (M+H)$^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
139		478.63	479	3.49 (4)	10A	30 (63)
140		466.63	467	2.33 (4)	10A	27 (58)
141		414.59	415	3.47 (4)	10A	11 (27)
142		453.58	454	2.27 (4)	12A	30 (66)
143		482.62	483	3.26 (4)	12A	32 (66)

Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
144		470.61	471	2.18 (4)	12A	31 (66)
145		499.66	500	2.65 (4)	13A	36 (72)
146		528.69	529	3.64 (4)	13A	38 (72)
147		516.69	517	2.47 (4)	13A	48 (93)
148		521.70	522	3.07 (1)	11A	37 (71)

Ex. No.	Structure	Molar mass	MS (EI): $(M+H)^+$	Retention time [min] (Method)	Reactant Ex. No.	Amount [mg] (Yield [% of theory])
149		408.54	409	3.7 (4)	8A	16.6 (41)
150		422.57	423	3.8 (3)	13A	25.5 (60)

Example 151

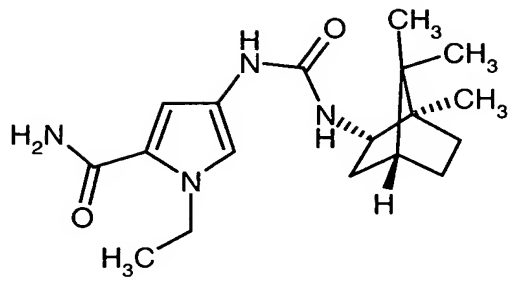
1-Ethyl-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxamide



40.0 mg (0.13 mmol) of 4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}-carbonyl)amino]-1H-pyrrole-2-carboxamide (Example 10) are dissolved in 1 ml of DMF, and 22.1 mg (0.20 mmol) of potassium tert-butoxide are added. After 5 minutes 10 µl (0.20 mmol) of bromoethane

Example 151

1-Ethyl-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxamide



40.0 mg (0.13 mmol) of 4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}-carbonyl)amino]-1H-pyrrole-2-carboxamide (Example 10) are dissolved in 1 ml of DMF, and 22.1 mg (0.20 mmol) of potassium tert-butoxide are added. After 5 minutes 10 µl (0.20 mmol) of bromoethane are added dropwise and the mixture is left with stirring at RT overnight. Subsequently the reaction mixture is purified by RP-HPLC. A solid is obtained.

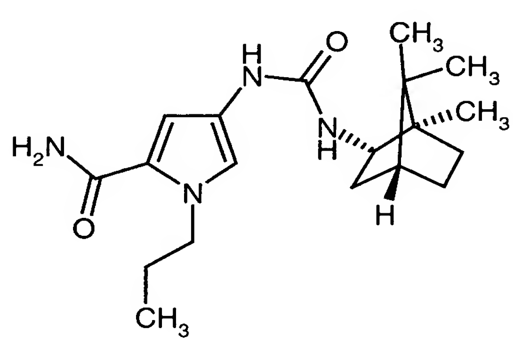
Yield: 11 mg (25% of theory)

LC-MS (Method 10): R_t = 3.31 min, MS (ESI^+): m/z = 333 $(M+H)^+$

^{1}H-NMR (300MHz, DMSO-d_6): δ = 7.79 (s, 1H), 7.26 (bs, 1H), 6.95 (d, 1H), 6.77 (bs, 1H), 6.51 (d, 1H), 5.95 (d, 1H), 4.24 (q, 2H), 3.87-3.98 (m, 1H), 2.14-2.28 (m, 1H), 1.54-1.77 (m, 3H), 1.09-1.33 (m, 5H), 0.90 (s, 3H), 0.84 (s, 3H), 0.73 (s, 3H), 0.69-0.78 (m, 1H).

Example 152

1-propyl-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxamide



3.5 mg (0.01 mmol) of 18-crown-6 are dissolved in 0.5 ml of DMF and then 40.0 mg (0.13 mmol) of 4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-

yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxamide (Example 10) and 17.3 mg (0.15 mmol) of potassium tert-butoxide are added. Subsequently a solution of 10 µl (0.16 mmol) of 1-bromopropane in 0.5 ml of DMF is added dropwise and the mixture is left with stirring at RT overnight. Subsequently the reaction mixture is purified by RP-HPLC. A solid is obtained.

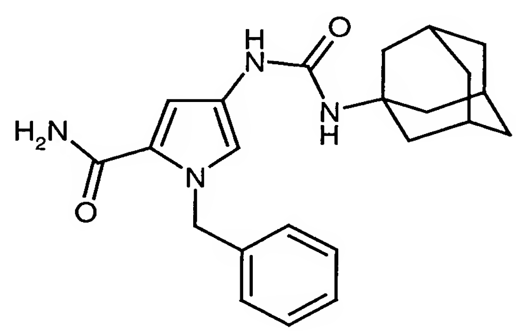
Yield: 14 mg (31% of theory)

LC-MS (Method 1): R_t = 2.75 min, MS (ESI^+): m/z = 347 $(M+H)^+$

^{1}H-NMR (300MHz, $CDCl_3$): δ = 6.83 (d, 1H), 6.46 (d, 1H), 5.84 (s, 1H), 5.46 (bs, 2H), 4.73 (d, 1H), 4.29 (t, 2H), 4.03-4.12 (m, 1H), 2.30-2.42 (m, 1H), 1.68-1.85 (m, 3H), 1.61-1.66 (m, 1H), 1.25-1.37 (m, 2H), 1.02-1.13 (m, 1H), 0.94 (s, 3H), 0.88 (t, 3H), 0.86 (s, 3H), 0.84 (s, 3H), 0.74 (dd, 1H).

Example 153

4-{[(1-adamantylamino)carbonyl]amino}-1-benzyl-1H-pyrrole-2-carboxamide



40 mg (0.16 mmol) of 1-benzyl-4-nitro-1H-pyrrole-2-carboxamide (Example 5A) are dissolved in 1 ml of THF, and a spatula tip of Raney nickel and then 10 µl (0.24 mmol) of hydrazine hydrate are added. The reaction mixture is stirred vigorously at RT for 1 h. It is filtered over kieselguhr and the solid product is washed with ethyl acetate. The filtrate is washed with sodium chloride solution, then dried over magnesium sulfate and freed from the solvent under reduced pressure. The residue obtained is dissolved in 1 ml of THF. Following the addition of 35 mg (0.20 mmol) of adamantyl isocyanate the mixture is stirred at RT for 1 h. The reaction mixture is purified by RP-HPLC. A solid is obtained.

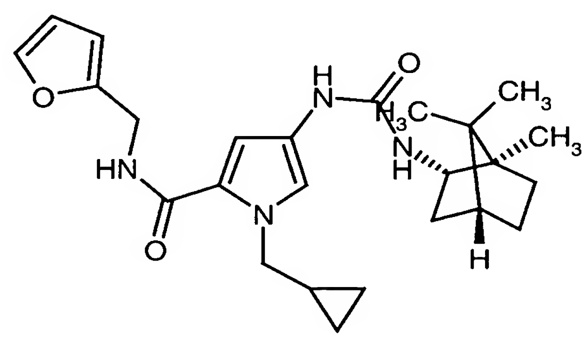
Yield: 58 mg (90% of theory)

LC-MS (Method 5): R_t = 2.23 min, MS (ESI$^+$): m/z = 393 $(M+H)^+$

^{1}H-NMR (300MHz, DMSO-d_6): δ = 7.81 (s, 1H), 7.35 (bs, 1H), 7.17-7.32 (m, 3H), 7.06-7.13 (m, 2H), 7.00 (d, 1H), 6.80 (bs, 1H), 6.55 (d, 1H), 5.62 (s, 1H), 5.51 (s, 2H), 2.00 (m, 3H), 1.89 (m, 6H), 1.61 (m, 6H).

Example 154

1-(cyclopropylmethyl)-*N*-(2-furylmethyl)-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1*H*-pyrrole-2-carboxamide



50 mg (0.13 mmol) of 1-(cyclopropylmethyl)-4-[({[(1R,2S,4R)-1,7,7-trimethyl-bicyclo-[2.2.1]hept-2-yl]amino}carbonyl)amino]-1*H*-pyrrole-2-carboxylic acid are dissolved in 4 ml of dimethylformamide at RT, and 24 mg (0.19 mmol) of *N,N*-dimethylpyridine-4-amine and 98 mg (0.26 mmol) of O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate are added. After 10 minutes 25 mg (0.259 mmol) of (2-furylmethyl)amine are added dropwise. The mixture is stirred at RT for 16 hours. The reaction solution is diluted with dimethyl sulfoxide and purified by means of preparative HPLC (Method 11).

Yield: 50 mg (88% of theory)

LC-MS (Method 1): R_t = 3.17 min

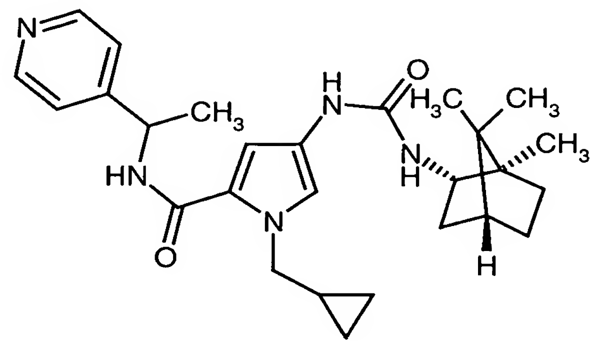
MS (ESIpos): m/z = 439 $(M+H)^+$

^{1}H-NMR (300MHz, DMSO-d_6) δ = 0.23-0.31 (m, 2H), 0.37-0.50 (m, 2H), 0.73 (s, 3H), 0.75-0.79 (m, 1H), 0.84 (s, 3H), 0.90 (s, 3H), 1.08-1.33 (m, 3H), 1.53-1.75 (m, 3H), 2.15-

2.29 (m, 1H), 3.79-3.98 (m, 1H), 4.09 (dd, 2H), 4.35 (d, 2H), 5.98 (d, 1H), 6.21 (d, 1H), 6.37-6.39 (m, 1H), 6.57 (d, 1H), 7.00 (d, 1H), 7.54 (s, 1H), 7.81 (s, 1H), 8.34 (t, 1H).

Example 155

1-(cyclopropylmethyl)-*N*-(1-pyridin-4-ylethyl)-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1*H*-pyrrole-2-carboxamide



50 mg (0.13 mmol) of 1-(cyclopropylmethyl)-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1*H*-pyrrole-2-carboxylic acid are dissolved in 4 ml of dimethylformamide at RT, and 24 mg (0.19 mmol) of *N,N*-dimethylpyridine-4-amine and 98 mg (0.26 mmol) of O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate are added. After 10 minutes 32 mg (0.26 mmol) of (1-pyridin-4-ylethyl)amine are added dropwise. The mixture is stirred at RT for 16 hours. The reaction solution is diluted with dimethyl sulfoxide and purified by means of preparative HPLC (Method 11).

Yield: 40 mg (61% of theory)

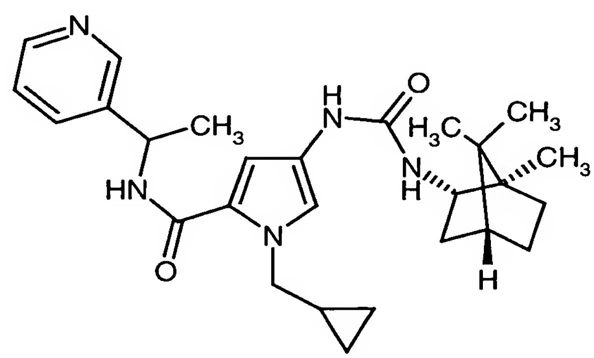
LC-MS (Method 1): R_t = 2.38 min

MS (ESIpos): m/z = 464 $(M+H)^+$

^{1}H-NMR (300MHz, DMSO-d_6) δ = 0.20-0.26 (m, 2H), 0.32-0.43 (m, 2H), 0.73 (s, 3H), 0.76-0.83 (m, 1H), 0.85 (s, 3H), 0.90 (s, 3H), 0.98-1.32 (m, 3H), 1.50 (d, 3H), 1.56-1.79 (m, 3H), 2.16-2.29 (m, 1H), 3.79-4.19 (m, 3H), 5.15-5.26 (m, 1H), 6.24 (bs, 1H), 6.87 (d, 1H), 8.01 (d, 1H), 8.09 (bs, 1H), 8.85 (d, 1H).

Example 156

1-(cyclopropylmethyl)-*N*-(1-pyridin-3-ylethyl)-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1*H*-pyrrole-2-carboxamide



50 mg (0.13 mmol) of 1-(cyclopropylmethyl)-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1*H*-pyrrole-2-carboxylic acid are dissolved in 4 ml of dimethylformamide at RT, and 24 mg (0.19 mmol) of *N,N*-dimethylpyridine-4-amine and 98 mg (0.26 mmol) of O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate are added. After 10 minutes 32 mg (0.26 mmol) of (1-pyridin-3-ylethyl)amine are added dropwise. The mixture is stirred at RT for 16 hours. The reaction solution is diluted with dimethyl sulfoxide and purified by means of preparative HPLC (Method 11).

Yield: 57 mg (95% of theory)

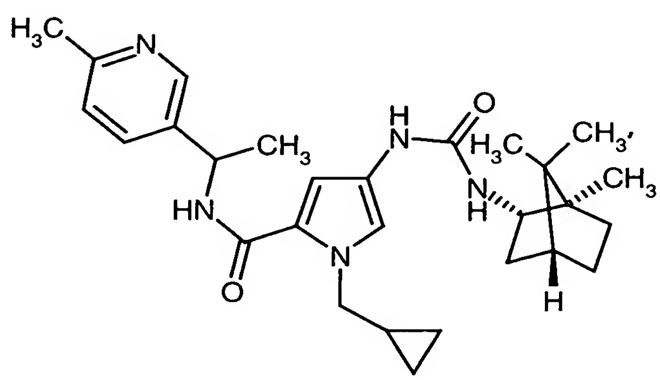
LC-MS (Method 1): $R_t = 2.48$ min

MS (ESIpos): m/z = 464 $(M+H)^+$

^{1}H-NMR (300MHz, DMSO-d_6) δ = 0.12-0.26 (m, 2H), 0.32-0.43 (m, 2H), 0.73 (s, 3H), 0.76-0.81 (m, 1H), 0.85 (s, 3H), 0.90 (s, 3H), 1.02-1.39 (m, 3H), 1.52 (d, 3H), 1.56-1.74 (m, 3H), 2.16-2.29 (m, 1H), 3.88-4.12 (m, 3H), 5.15-5.28 (m, 1H), 6.23 (bs, 1H), 6.80 (d, 1H), 6.98 (d, 1H), 8.00-8.09 (m, 2H), 8.50 (d, 1H), 8.56 (d, 1H), 8.80 (d, 1H) 8.90 (d, 1H).

Example 157

1-(cyclopropylmethyl)-*N*-[1-(6-methylpyridin-3-yl)ethyl]-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1*H*-pyrrole-2-carboxamide



50 mg (0.13 mmol) of 1-(cyclopropylmethyl)-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1H-pyrrole-2-carboxylic acid are dissolved in 4 ml of dimethylformamide at RT, and 24 mg (0.19 mmol) of *N,N*-dimethylpyridine-4-amine and 98 mg (0.26 mmol) of O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate are added. After 10 minutes 35 mg (0.26 mmol) of 1-(6-methylpyridin-3-yl)ethyl]amine are added dropwise. The mixture is stirred at RT for 16 hours. The reaction solution is diluted with dimethyl sulfoxide and purified by means of preparative HPLC (Method 11).

Yield: 6 mg (10% of theory)

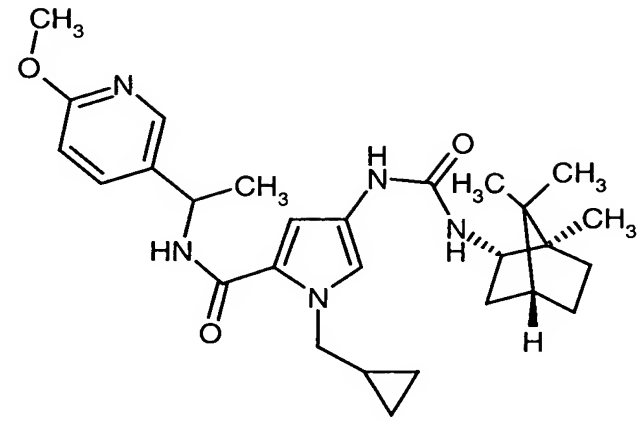
LC-MS (Method 10): R_t = 3.04 min

MS (ESIpos): m/z = 478 $(M+H)^+$

^{1}H-NMR (300MHz, DMSO-d_6) δ = 0.12-0.27 (m, 2H), 0.33-0.42 (m, 2H), 0.73 (s, 3H), 0.76-0.83 (m, 1H), 0.85 (s, 3H), 0.90 (s, 3H), 1.01-1.35 (m, 3H), 1.46-1.78 (m, 6H), 2.14-2.29 (m, 1H), 2.72 (s, 3H), 3.89-4.11 (m, 3H), 5.13-5.27 (m, 1H), 6.16 (bs, 1H), 6.79 (d, 1H), 6.97 (d, 1H), 7.95-8.05 (m, 1H), 8.39-8.48 (m, 2H).

Example 158

1-(cyclopropylmethyl)-*N*-[1-(6-methoxypyridin-3-yl)ethyl]-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1*H*-pyrrole-2-carboxamide



50 mg (0.13 mmol) of 1-(cyclopropylmethyl)-4-[({[(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]amino}carbonyl)amino]-1*H*-pyrrole-2-carboxylic acid are dissolved in 4 ml of dimethylformamide at RT, and 24 mg (0.19 mmol) of *N,N*-dimethylpyridine-4-amine and 98 mg (0.26 mmol) of O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate are added. After 10 minutes 32 mg (0.26 mmol) of [1-(6-methoxypyridin-3-yl)ethyl]amine are added dropwise. The mixture is stirred at RT for 16 hours. The reaction solution is diluted with dimethyl sulfoxide and purified by means of preparative HPLC (Method 11).

Yield: 63 mg (99% of theory)

LC-MS (Method 4): R_t = 3.42 min

MS (ESIpos): m/z = 494 $(M+H)^+$

^{1}H-NMR (300MHz, DMSO-d_6) δ = 0.21-0.43 (m, 4H), 0.73 (s, 3H), 0.75-0.81 (m, 1H), 0.84 (s, 3H), 0.90 (s, 3H), 1.02-1.39 (m, 3H), 1.43 (d, 3H), 1.56-1.76 (m, 3H), 2.09-2.29 (m, 1H), 3.80-4.11 (m, 3H), 3.83 (s, 3H), 4.95-5.16 (m, 1H), 6.15 (bs, 1H), 6.69 (d, 1H), 6.83 (d, 1H), 6.96 (d, 1H), 7.76 (dd, 2H), 7.95 (bs, 1H), 8.14 (d, 1H), 8.27 (d, 1H).

<u>B. Evaluation of the physiological activity</u>

The *in vitro* action of the compounds of the invention can be shown in the following assays:

Anti-HCMV (anti-human cytomegalovirus) cytopathogenicity tests

The test compounds are used as 50 millimolar (mM) solutions in dimethyl sulfoxide (DMSO). Ganciclovir, foscarnet and cidofovir serve as reference compounds. Following the addition of 2 µl in each case of the 50, 5, 0.5 and 0.05 mM DMSO stock solutions to 98 µl portions of cell culture medium in row 2 A-H in duplicate determination, 1:2 dilutions are carried out with 50 µl portions of medium up to row 11 of the 96-well plate. The wells in rows 1 and 12 contain 50 µl of each medium. Then 150 µl portions of a suspension of 1 x 10^4 cells (human prepuce fibroblasts [NHDF]) are pipetted into the wells (row 1 = cell control) and a mixture of HCMV-infected and uninfected NHDF cells (M.O.I. = 0.001 – 0.002), i.e. 1-2 infected cells per 1000 uninfected cells, is pipetted into rows 2-12. Row 12 (without substance) serves as virus control. The final test concentrations are 250 – 0.0005 µM. The plates are incubated at 37°C/5% CO_2 for 6 days, i.e. until all the cells are infected in the virus controls (100% cytopathogenic effect [CPE]). The wells are then fixed and stained by adding a mixture of formalin and Giemsa's dye (30 minutes), washed with double-distilled water and dried in a drying oven at 50°C. Thereafter the plates are evaluated visually using an overhead microscope (Plaque multiplier from Technomara).

The following data can be acquired from the test plates:

CC_{50} (NHDF) = substance concentration in µM, at which no visible cytostatic effects on the cells are evident by comparison with the untreated cell control;

EC_{50} (HCMV) = substance concentration in µM which inhibits the CPE (cytopathic effect) by 50% compared with the untreated virus control;

SI (selectivity index) = CC_{50} (NHDF) / EC_{50} (HCMV).

Representative in vitro activity data for the compounds of the invention are shown in Table A:

Table A

Example No.	NHDF CC_{50} [µM]	HCMV EC_{50} [nM]	SI HCMV
3	25	60	417
4	12	86	139
6	125	80	1389
7	35	40	875
24	25	5.8	6552
60	50	7	7143
73	38	1.9	20 000
98	50	4	6025
99	50	5.8	8621
131	50	1.9	26 316
133	25	1.9	13 158

The suitability of the compounds of the invention for treating HCMV infections can be demonstrated in the following animal model:

HCMV Xenograft Gelfoam® model

Animals:

3-4-week-old female immunodeficient mice (16-18 g), Fox Chase SCID or Fox Chase SCID-NOD or SCID beige, are purchased from commercial breeders (Bomholtgaard, Jackson). The animals are kept under sterile conditions (including bedding and feed) in isolators.

Virus growing:

Human cytomegalovirus (HCMV), Davis strain, is grown *in vitro* on human embryonic prepuce fibroblasts (NHDF cells). After the NHDF cells have been infected with a

multiplicity of infection (M.O.I) of 0.01, the virus-infected cells are harvested 5-7 days later and stored in the presence of minimal essential medium (MEM), 10% fetal calf serum (FCS) with 10% DMSO at -40°C. After serial ten-fold dilutions of the virus-infected cells, the titer is determined on 24-well plates of confluent NHDF cells after vital staining with neutral red, or fixing and staining with a formalin-giemsa mixture (as described under B.).

<u>Preparation of the sponges, transplantation, treatment and evaluation:</u>

Collagen sponges 1 x 1 x 1 cm in size (Gelfoam®; Peasel & Lorey, Order No. 407534; K.T. Chong et al., Abstracts of 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, 1999, p. 439; P.M. Kraemer et al., Cancer Research 1983, (43): 4822-4827) are initially wetted with phosphate-buffered saline (PBS), with the trapped air bubbles being removed by degassing, and then are stored in MEM + 10% FCS. 1 x 10^6 virus-infected NHDF cells (infection with HCMV Davis M.O.I = 0.01) are detached 3 hours after infection and applied dropwise, in 20 µl MEM, 10% FCS, to a moist sponge. Optionally, after 12-13 hours, 5 ng/µl basic fibroblast growth factor (bFGF) in 25 µl of PBS/0.1% BSA/1 mM DTT are applied to the infected sponges, and incubation is carried out for 1 hour. For the transplantation, the immunodeficient mice are anaesthetized with Avertin or an azepromazine/xylazine and ketamine mixture, the fur on the back is removed using a dry shaver, the epidermis is opened 1-2 cm and destressed, and the moist sponges are transplanted under the dorsal skin. The surgical wound is closed with tissue glue. 24 hours after the transplantation, the mice are treated orally with the substance three times a day (7.00 h and 14.00 h and 19.00 h) twice a day (8.00 h and 17.00 h), or once a day (14.00 h) over a period of 8 days. The daily dose is 3 or 10 or 30 or 100 mg/kg of body weight, the application volume is 10 ml/kg of body weight. The substances are formulated as a 0.5% Tylose suspension optionally with 2% DMSO. 9 days after transplantation and 16 hours after the last administration of the substance, the animals are painlessly sacrificed and the sponge is removed. The virus-infected cells are released from the sponge by collagenase digestion (330 U/1.5 ml) and stored in the presence of MEM, 10% fetal calf serum, 10% DMSO at -140°C. Evaluation takes place after serial ten-fold dilution of the virus-infected cells by determination of the titer on 24-well plates of confluent NHDF cells after vital staining with neutral red, or after fixing and staining with a formalin-giemsa mixture (as described under B.). The parameter determined is the number of infectious virus particles after treatment with the substance, in comparison with the placebo-treated control group.

C. Exemplary embodiments of pharmaceutical compositions

The compounds of the invention can be converted into pharmaceutical preparations as follows:

Tablet:

Composition:

100 mg of the compound of Example 1, 50 mg of lactose (monohydrate), 50 mg of corn starch (native), 10 mg of polyvinylpyrolidone (PVP 25) (BASF, Ludwigshafen, Germany) and 2 mg of magnesium stearate.

Tablet weight 212 mg. Diameter 8 mm, radius of curvature 12 mm.

Production:

The mixture of active ingredient, lactose and starch is granulated with a 5% strength solution (m/m) of the PVP in water. The granules, after drying, are mixed with the magnesium stearate for 5 minutes. This mixture is compressed using a conventional tableting press (for tablet format see above). A guideline for the compressive force used for compression is 15 kN.

Suspension for oral administration:

Composition:

1000 mg of the compound from Example 1, 1000 mg of ethanol (96%), 400 mg of Rhodigel (xanthan gum from FMC, Pennsylvania, USA) and 99 g of water.

10 ml of oral suspension correspond to a single dose of 100 mg of the compound of the invention.

Production:

The Rhodigel is suspended in ethanol and the active ingredient is added to the suspension. The water is added with stirring. Stirring is carried out for about 6 h until the swelling of the Rhodigel is at an end.